JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 65, NO. 6, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jacc.2014.12.021

HIGHLIGHTS OF THE YEAR

Editor-in-Chief's Picks From 2014: Part One

Valentin Fuster, MD, PhD

As I spent countless hours pouring over hundreds of manuscripts to select those that rose to the top over the past year, I became incredibly excited about being part of a *Journal* that produces such wonderfully rich and diverse content each year. I have personally selected the papers (both original investigations and review articles) from 13 distinct specialties for your review. There are approximately 150 articles selected across this 2-part series, which represents less than 3% of the papers submitted to *JACC* in 2014. In order to present the full breadth of this important research in a consumable fashion, we will present these manuscripts over the course of 2 issues of *JACC*.

Part One includes the sections: Congenital Heart Disease, Coronary Disease & Interventions, Genetics, Omics, & Tissue Regeneration, CV Prevention & Health Promotion, Cardiac Failure, and Cardiomyopathies (1–70). Part Two includes the sections: Hypertension, Imaging, Metabolic Disorders & Lipids, Neurovascular & Neurodegenerative Disorders, Rhythm Disorders, Valvular Heart Disease, and Vascular Medicine.

CONGENITAL HEART DISEASE

Procedural Results and Safety of Common Interventional Procedures in Congenital Heart Disease: Initial Report From the National Cardiovascular Data Registry

J.W. Moore, et al.

BACKGROUND The National Cardiovascular Data Registry (NCDR) launched the IMPACT (Improving Pediatric and Adult Congenital Treatment) Registry in 2010. By 2013, its patient enrollment exceeded that of other current and historical congenital catheterization registries.

OBJECTIVES This study sought to describe procedural results and safety of 6 common congenital interventions performed in patients enrolled during the IMPACT Registry's initial periods.

METHODS With specified exclusions, we compiled registry data from patients enrolled in the IMPACT Registry from January 2011 through March 2013 who underwent 1 of the following isolated procedures: device closure of atrial septal defect (ASD); device closure of patent ductus arteriosus (PDA); pulmonary valvuloplasty; aortic valvuloplasty; coarctation of the aorta angioplasty and stenting; and pulmonary artery stenting. Patient data, procedural data and results, and adverse events (AEs) were reviewed and described.

RESULTS In 4,152 catheterizations, 1 isolated procedure was reported. There were 1,286 single-ASD procedures, 1,375 PDA procedures, 270 "typical" pulmonary valve procedures, 305 aortic valve procedures, 671 aortic procedures, and 245 pulmonary artery procedures. The reported procedure was performed in >95% of catheterizations. Stated outcomes were accomplished in >98% of ASD and PDA procedures, but less commonly in the others, with coarctation angioplasty procedures being the least successful (51%). Reported major AE rates ranged from 0% to 3.3%; total AE rates ranged from 5.3% to 24.3%.

CONCLUSIONS Contemporary community practice, procedural outcomes, and safety for 6 common congenital interventional procedures are reported. These benchmarks may be compared with individual center results and historical single-center and multicenter results (1).

Low Risk of Pulmonary Valve Implantation After a Policy of Transatrial Repair of Tetralogy of Fallot Delayed Beyond the Neonatal Period: The Melbourne Experience Over 25 Years

Y. d'Udekem, et al.

OBJECTIVES The study sought to evaluate the late outcomes of a policy of transatrial repair delayed beyond the neonatal period.

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You can also listen to this issue's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

BACKGROUND Long-term outcomes of transatrial repair of tetralogy of Fallot are unknown.

METHODS The records of 675 consecutive patients undergoing a transatrial repair of tetralogy of Fallot between 1980 and 2005 were reviewed, their follow-up updated and survival confirmed from national death registries. One-third (220 of 675) had undergone previous palliation. Median age at repair was 2 years in the first 8 years, and 1 year from 1988 onward. A transannular incision was performed in 75% of cases and autologous pericardium was the material used to patch this incision in 92% of cases.

RESULTS There were 7 hospital deaths (1%). Eight patients died during follow-up (2 sudden unexpected and 6 noncardiac deaths). Mean follow-up was 11.7 ± 6.3 years. Twenty-five years' survival was 97% (95% confidence interval [CI]: 95% to 98%). Twenty-five years' freedom from implantation of a valved conduit was 84.6% (95% CI: 77.8% to 89.5%). By multivariable analysis, prior palliation and younger age at repair were predictive of implantation of a valved conduit (hazard ratio: 2.4, 95% CI: 1.3 to 4.6, $p = 0.008$; hazard ratio: 0.70, 95% CI: 0.50 to 0.96, $p = 0.03$, respectively).

CONCLUSIONS During long-term follow-up, transatrial repair of tetralogy of Fallot was associated with a minimal risk of sudden death and low rate of re-intervention for right ventricular dilation and residual outflow tract obstruction (2).

D-Transposition of the Great Arteries: The Current Era of the Arterial Switch Operation

J. Villafañe, et al.

This paper aims to update clinicians on "hot topics" in the management of patients with D-loop transposition of the great arteries (D-TGA) in the current surgical era. The arterial switch operation (ASO) has replaced atrial switch procedures for D-TGA, and 90% of patients now reach adulthood. The Adult Congenital and Pediatric Cardiology Council of the American College of Cardiology assembled a team of experts to summarize current knowledge on genetics, pre-natal diagnosis, surgical timing, balloon atrial septostomy, prostaglandin E_1 therapy, intraoperative techniques, imaging, coronary obstruction, arrhythmias, sudden death, neoaortic regurgitation and dilation, neurodevelopmental (ND) issues, and lifelong care of D-TGA patients. In simple D-TGA: 1) familial recurrence risk is low; 2) children diagnosed pre-natally have improved cognitive skills compared with those diagnosed post-natally; 3) echocardiography helps to identify risk factors; 4) routine use of BAS and prostaglandin E_1 may not be indicated in all cases; 5) early ASO improves outcomes and reduces costs with a low mortality; 6) single or intramural coronary arteries remain risk factors; 7) post-ASO arrhythmias and cardiac dysfunction should raise suspicion of coronary insufficiency; 8) coronary insufficiency and arrhythmias are rare but are associated with sudden death; 9) early- and late-onset ND abnormalities are common; 10) aortic regurgitation and aortic root dilation are well tolerated; and 11) the aging ASO patient may benefit from "exercise-prescription" rather than restriction. Significant strides have been made in understanding risk factors for cardiac, ND, and other important clinical outcomes after ASO (3).

Survival Differences in Pediatric Pulmonary Arterial Hypertension: Clues to a Better Understanding of Outcome and Optimal Treatment Strategies

W.M.H. Zijlstra, et al.

OBJECTIVES In order to describe survival and treatment strategies in pediatric pulmonary arterial hypertension (PAH) in the current era of PAH-targeted drugs and to identify predictors of outcome, we studied uniformly defined contemporary patient cohorts at 3 major referral centers for pediatric PAH (New York [NY], Denver, and the Netherlands [NL]).

BACKGROUND In pediatric PAH, discrepancies exist in reported survival rates between North American and European patient cohorts, and robust data for long-term treatment effects are lacking.

METHODS According to uniform inclusion criteria, 275 recently diagnosed consecutive pediatric PAH patients who visited the 3 referral centers between 2000 and 2010 were included.

RESULTS Unadjusted survival rates differed between the center cohorts (1-, 3-, and 5-year transplantation-free survival rates: 100%, 96%, and 90% for NY; 95%, 87%, and 78% for Denver; and 84%, 71%, and 62% for NL, respectively; $p < 0.001$). Based on World Health Organization (WHO) functional class and hemodynamic parameters, disease severity at diagnosis differed between the center cohorts. Adjustment for diagnosis, WHO functional class, indexed pulmonary vascular resistance, and pulmonary-to-systemic arterial pressure ratio resolved the observed survival differences. Treatment with PAH-targeted dual and triple therapy during the study period was associated with better survival than treatment with PAH-targeted monotherapy.

CONCLUSIONS Survival rates of pediatric PAH patients differed between 3 major referral centers. This could be explained by differences between the center cohorts in patients' diagnoses and measures of disease severity,

which were identified as important predictors of outcome. In this study, treatment with PAH-targeted combination therapy during the study period was independently associated with improved survival (4).

Clinical Outcomes and Improved Survival in Patients With Protein-Losing Enteropathy After the Fontan Operation

A.S. John, et al.

BACKGROUND Patients with protein-losing enteropathy (PLE) following the Fontan operation have a reported 50% mortality at 5 years after diagnosis.

OBJECTIVES The aim of this study was to review outcomes in patients with PLE following the Fontan operation.

METHODS From 1992 to 2010, 42 patients (55% male) with PLE following the Fontan operation were identified from clinical databases at the Mayo Clinic. Data were collected retrospectively.

RESULTS Mean age at PLE diagnosis was 18.9 ± 11.0 years. Initial Fontan operation was performed at 10.1 ± 10.8 years of age. Mean time from Fontan operation to PLE diagnosis was 8.4 ± 14.2 years. Survival was 88% at 5 years. Decreased survival was seen in patients with high Fontan pressure (mean >15 mm Hg; $p = 0.04$), decreased ventricular function (ejection fraction <55%; $p = 0.03$), and New York Heart Association functional class >2 at diagnosis ($p = 0.04$). Patients who died had higher pulmonary vascular resistance (3.8 ± 1.6 Wood units [WU] vs. 2.1 ± 1.1 WU; $p = 0.017$), lower cardiac index (1.6 ± 0.4 l/min/m^2 vs. 2.7 ± 0.7 l/min/m^2; $p < 0.0001$), and lower mixed venous saturation (53% vs. 66%; $p = 0.01$), compared with survivors. Factors were assessed at the time of PLE diagnosis. Treatments used more frequently in survivors with PLE included spironolactone (21 [68%]), octreotide (7 [21%]), sildenafil (6 [19%]), fenestration creation (15 [48%]), and relief of Fontan obstruction (7 [23%]).

CONCLUSIONS PLE remains difficult to treat; however, in the current era, survival has improved with advances in treatment. Further study is needed to better understand the mechanism of disease and ideal treatment strategy (5).

CORONARY DISEASE & INTERVENTIONS

The Year in Acute Coronary Syndrome

R.P. Giugliano, et al.

In this year's report on acute coronary syndromes (ACS), we have expanded the scope to include ST-segment elevation myocardial infarction (STEMI) in addition to non-ST-segment elevation ACS. In this report, we review selected highlights across the spectrum of ACS published between June 2012 and September 2013 (6).

Undetectable High-Sensitivity Cardiac Troponin T Level in the Emergency Department and Risk of Myocardial Infarction

N. Bandstein, et al.

OBJECTIVES This study sought to evaluate if an undetectable (<5 ng/l) high-sensitivity cardiac troponin T (hs-cTnT) level and an electrocardiogram (ECG) without signs of ischemia can rule out myocardial infarction (MI) in the emergency department (ED).

BACKGROUND Chest pain is a common symptom often associated with benign conditions, but may be a sign of MI. Because there is no rapid way to rule out MI, many patients are admitted to the hospital.

METHODS All patients who sought medical attention for chest pain and had at least 1 hs-cTnT analyzed during 2 years at the Karolinska University Hospital, Stockholm, Sweden, were included. We calculated the negative predictive values of an undetectable hs-cTnT and ECG without ischemia for MI and death within 30 days.

RESULTS We included 14,636 patients, of whom 8,907 (61%) had an initial hs-cTnT of <5 ng/l; 21% had 5 to 14 ng/l, and 18% had >14 ng/l. During 30-day follow-up, 39 (0.44%) patients with undetectable hs-cTnT had a MI, of whom 15 (0.17%) had no ischemic ECG changes. The negative predictive value for MI within 30 days in patients with undetectable hs-cTnT and no ischemic ECG changes was 99.8% (95% confidence interval [CI]: 99.7 to 99.9). The negative predictive value for death was 100% (95% CI: 99.9 to 100).

CONCLUSIONS All patients with chest pain who have an initial hs-cTnT level of <5 ng/l and no signs of ischemia on an ECG have a minimal risk of MI or death within 30 days, and can be safely discharged directly from the ED (7).

Long-Term Benefit of Early Pre-Reperfusion Metoprolol Administration in Patients With Acute Myocardial Infarction: Results From the METOCARD-CNIC Trial (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction)

G. Pizarro, et al.

OBJECTIVES The goal of this trial was to study the long-term effects of intravenous (IV) metoprolol administration before reperfusion on left ventricular (LV) function and clinical events.

BACKGROUND Early IV metoprolol during ST-segment elevation myocardial infarction (STEMI) has been shown to reduce infarct size when used in conjunction with primary percutaneous coronary intervention (pPCI).

METHODS The METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial recruited 270 patients with Killip class ≤II anterior STEMI presenting early after symptom onset (<6 h) and randomized them to pre-reperfusion IV metoprolol or control group. Long-term magnetic resonance imaging (MRI) was performed on 202 patients (101 per group) 6 months after STEMI. Patients had a minimal 12-month clinical follow-up.

RESULTS Left ventricular ejection fraction (LVEF) at the 6 months MRI was higher after IV metoprolol (48.7 ± 9.9% vs. 45.0 ± 11.7% in control subjects; adjusted treatment effect 3.49%; 95% confidence interval [CI]: 0.44% to 6.55%; p = 0.025). The occurrence of severely depressed LVEF (≤35%) at 6 months was significantly lower in patients treated with IV metoprolol (11% vs. 27%, p = 0.006). The proportion of patients fulfilling Class I indications for an implantable cardioverter-defibrillator (ICD) was significantly lower in the IV metoprolol group (7% vs. 20%, p = 0.012). At a median follow-up of 2 years, occurrence of the pre-specified composite of death, heart failure admission, reinfarction, and malignant arrhythmias was 10.8% in the IV metoprolol group versus 18.3% in the control group, adjusted hazard ratio (HR): 0.55; 95% CI: 0.26 to 1.04; p = 0.065. Heart failure admission was significantly lower in the IV metoprolol group (HR: 0.32; 95% CI: 0.015 to 0.95; p = 0.046).

CONCLUSIONS In patients with anterior Killip class ≤II STEMI undergoing pPCI, early IV metoprolol before reperfusion resulted in higher long-term LVEF, reduced incidence of severe LV systolic dysfunction and ICD indications, and fewer heart failure admissions. (Effect of METOprolol in CARDioproteCtioN During an Acute Myocardial InfarCtion. The METOCARD-CNIC Trial; NCT01311700) (8).

Short- and Long-Term Cause of Death in Patients Treated With Primary PCI for STEMI

F. Pedersen, et al.

BACKGROUND Short-term mortality has been studied thoroughly in patients undergoing primary percutaneous coronary intervention (PCI), whereas long-term cause of death in patients with ST-segment elevation myocardial infarction (STEMI) remains unknown.

OBJECTIVES The goal of this study was to describe the association between time and cause of death in patients with STEMI undergoing primary PCI.

METHODS A centralized civil registration system, patient files, and public disease and death cause registries with an accurate record linkage were used to trace time and cause of death in 2,804 consecutive patients with STEMI (age 63 ± 13 years, 72% males) treated with primary PCI.

RESULTS Patients were followed up for a median of 4.7 years. During a total of 13,447 patient-years, 717 patients died. Main causes of death within the first 30 days were cardiogenic shock and anoxic brain injury after cardiac arrest. Age, culprit vessel size and flow, and the presence of heart failure and diabetes were independent predictors of mortality. After 30 days, the annual cardiac mortality rate was <1.5%. Causes of death beyond 30 days were noncardiac in 65% of cases (mainly malignancies and pulmonary diseases). The 30-day, 1-year, and 5-year all-cause (and cardiac) mortality rates were 7.9% (7.3%), 11.4% (8.4%), and 23.3% (13.8%), respectively.

CONCLUSIONS Patients who survive the first month after an STEMI treated with primary PCI have an excellent prognosis, with a <1.5% annual risk of successive cardiac death. Noncardiac causes are responsible for the majority of later deaths in these patients (9).

A Polypill Strategy to Improve Global Secondary Cardiovascular Prevention: From Concept to Reality

J.M. Castellano, et al.

The prevention of cardiovascular disease (CVD) by using a polypill has gained increasing momentum as a strategy to contain progression of the disease. Since its initial conception just over a decade ago, only a handful of trials have been completed assessing the efficacy and safety of this innovative concept. The results of these trials have supported the viability of the polypill in CVD prevention and management, albeit with a few caveats, essentially related to the lack of evidence on the effect of the polypill to effectively reduce cardiovascular events. The polypill has the potential to control the global health epidemic of CVD by effectively reaching underdeveloped regions of the world, simplifying healthcare delivery, improving cost-effectiveness, increasing medication adherence, and supporting a comprehensive prescription of evidence-based cardioprotective drugs. Major trials underway will provide definitive evidence on the efficacy of the polypill in reducing cardiovascular events in a

cost-effective manner. The results of these studies will determine whether a polypill strategy can quell the burgeoning public health challenge of CVD and will potentially provide the evidence to implement an effective, simple, and innovative solution to restrain the global CVD pandemic (10).

Prognostic Value of Fractional Flow Reserve: Linking Physiologic Severity to Clinical Outcomes

N.P. Johnson, et al.

BACKGROUND Fractional flow reserve (FFR) has become an established tool for guiding treatment, but its graded relationship to clinical outcomes as modulated by medical therapy versus revascularization remains unclear.

OBJECTIVES The study hypothesized that FFR displays a continuous relationship between its numeric value and prognosis, such that lower FFR values confer a higher risk and therefore receive larger absolute benefits from revascularization.

METHODS Meta-analysis of study- and patient-level data investigated prognosis after FFR measurement. An interaction term between FFR and revascularization status allowed for an outcomes-based threshold.

RESULTS A total of 9,173 (study-level) and 6,961 (patient-level) lesions were included with a median follow-up of 16 and 14 months, respectively. Clinical events increased as FFR decreased, and revascularization showed larger net benefit for lower baseline FFR values. Outcomes-derived FFR thresholds generally occurred around the range 0.75 to 0.80, although limited due to confounding by indication. FFR measured immediately after stenting also showed an inverse relationship with prognosis (hazard ratio: 0.86, 95% confidence interval: 0.80 to 0.93; $p < 0.001$). An FFR-assisted strategy led to revascularization roughly half as often as an anatomy-based strategy, but with 20% fewer adverse events and 10% better angina relief.

CONCLUSIONS FFR demonstrates a continuous and independent relationship with subsequent outcomes, modulated by medical therapy versus revascularization. Lesions with lower FFR values receive larger absolute benefits from revascularization. Measurement of FFR immediately after stenting also shows an inverse gradient of risk, likely from residual diffuse disease. An FFR-guided revascularization strategy significantly reduces events and increases freedom from angina with fewer procedures than an anatomy-based strategy (11).

Impact of Microvascular Obstruction on the Assessment of Coronary Flow Reserve, Index of Microcirculatory Resistance, and Fractional Flow Reserve After ST-Segment Elevation Myocardial Infarction

F. Cuculi, et al.

BACKGROUND Invasive assessment of coronary physiology (IACP) offers important prognostic insights in ST-segment elevation myocardial infarction (STEMI) but the dynamics of coronary recovery are poorly understood.

OBJECTIVES This study sought to examine the evolution of coronary flow reserve (CFR), index of microcirculatory resistance (IMR), ratio of distal coronary pressure (Pd) to mean aortic pressure (Pa), and fractional flow reserve (FFR) in patients undergoing primary percutaneous coronary intervention (PPCI).

METHODS 82 patients with STEMI underwent IACP at PPCI. Repeat IACP was performed in 61 patients (74%) at day 1 and in 46 patients (56%) at 6 months. Contrast-enhanced cardiac magnetic resonance imaging (CMR) was performed in 45 patients (55%) at day 1 and in 41 patients (50%) at 6 months. Changes in IACP were compared between patients with and without microvascular obstruction (MVO) on CMR.

RESULTS MVO was present in 21 of 45 patients (47%). Patients with MVO had lower CFR at PPCI and day 1 ($p < 0.05$) and a trend toward higher IMR values ($p = 0.07$). At 6 months, CFR and IMR were not significantly different between the groups. Baseline flow and Pd/Pa remained stable over time but FFR reduced significantly between PPCI and 6 months ($p = 0.008$); this reduction was mainly observed in patients with MVO ($p = 0.006$) but not in those without MVO ($p = 0.21$).

CONCLUSIONS In PPCI-treated patients with STEMI, coronary microcirculation begins to recover within 24 h and recovery progresses further by 6 months. FFR significantly reduces from baseline to 6 months. The presence of MVO indicates a highly dysfunctional microcirculation (12).

ST-Segment Elevation Myocardial Infarction Treated by Radial or Femoral Approach in a Multicenter Randomized Clinical Trial: The STEMI-RADIAL Trial

I. Bernat, et al.

OBJECTIVES This study sought to compare radial and femoral approaches in patients presenting with ST-segment elevation myocardial infarction (STEMI) and

undergoing primary percutaneous coronary intervention (PCI) by high-volume operators experienced in both access sites.

BACKGROUND The exact clinical benefit of the radial compared to the femoral approach remains controversial.

METHODS STEMI-RADIAL (ST Elevation Myocardial Infarction treated by RADIAL or femoral approach) was a randomized, multicenter trial. A total of 707 patients referred for STEMI <12 h of symptom onset were randomized in 4 high-volume radial centers. The primary endpoint was the cumulative incidence of major bleeding and vascular access site complications at 30 days. The rate of net adverse clinical events (NACE) was defined as a composite of death, myocardial infarction, stroke, and major bleeding/vascular complications. Access site crossover, contrast volume, duration of intensive care stay, and death at 6 months were secondary endpoints.

RESULTS The primary endpoint occurred in 1.4% of the radial group (n = 348) and 7.2% of the femoral group (n = 359; p = 0.0001). The NACE rate was 4.6% versus 11.0% (p = 0.0028), respectively. Crossover from radial to femoral approach was 3.7%. Intensive care stay (2.5 ± 1.7 days vs. 3.0 ± 2.9 days, p = 0.0038) as well as contrast utilization (170 ± 71 ml vs. 182 ± 60 ml, p = 0.01) were significantly reduced in the radial group. Mortality in the radial and femoral groups was 2.3% versus 3.1% (p = 0.64) at 30 days and 2.3% versus 3.6% (p = 0.31) at 6 months, respectively.

CONCLUSIONS In patients with STEMI undergoing primary PCI by operators experienced in both access sites, the radial approach was associated with significantly lower incidence of major bleeding and access site complications and superior net clinical benefit. These findings support the use of the radial approach in primary PCI as first choice after proper training. (Trial Comparing Radial and Femoral Approach in Primary Percutaneous Coronary Intervention [PCI] [STEMI-RADIAL]; NCT01136187) (13).

Ticagrelor Effects on Myocardial Infarction and the Impact of Event Adjudication in the PLATO (Platelet Inhibition and Patient Outcomes) Trial

K.W. Mahaffey, et al.

OBJECTIVES This study sought to report the treatment effect of ticagrelor on myocardial infarction (MI) and the strategy for and impact of event adjudication in the PLATO (Platelet Inhibition and Patient Outcomes) trial.

BACKGROUND In PLATO, ticagrelor reduced cardiovascular death, MI, or stroke in patients with acute coronary syndromes (ACS).

METHODS A clinical events committee (CEC) prospectively defined and adjudicated all suspected MI events, on the basis of events reported by investigators and by triggers on biomarkers. Treatment comparisons used CEC-adjudicated data, and per protocol, excluded silent MI.

RESULTS Overall, 1,299 (610 ticagrelor, 689 clopidogrel) MIs reported by the CEC occurred during the trial. Of these, 1,097 (504 ticagrelor, 593 clopidogrel) contributed to the primary composite endpoint. Site investigators reported 1,198 (580 ticagrelor, 618 clopidogrel) MIs. Ticagrelor significantly reduced overall MI rates (12-month CEC-adjudicated Kaplan-Meier rates: 5.8% ticagrelor, 6.9% clopidogrel; hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.75 to 0.95). Nonprocedural MI (HR: 0.86; 95% CI: 0.74 to 1.01) and MI related to percutaneous coronary intervention or stent thrombosis tended to be lower with ticagrelor. MIs related to coronary artery bypass graft surgery were few, but numerical excess was observed in patients assigned ticagrelor. Analyses of overall MIs using investigator-reported data showed similar results but did not reach statistical significance (HR: 0.88; 95% CI: 0.78 to 1.00).

CONCLUSIONS In patients with ACS, ticagrelor significantly reduced the incidence of MI compared with clopidogrel, with consistent results across most MI subtypes. CEC procedures identified more MI endpoints compared with site investigators. (A Comparison of Ticagrelor [AZD6140] and Clopidogrel in Patients With Acute Coronary Syndrome [PLATO]; NCT00391872) (14).

Coronary Stent Thrombosis With Vorapaxar Versus Placebo: Results From the TRA 2°P-TIMI 50 Trial

M.P. Bonaca, et al.

BACKGROUND Vorapaxar, a novel thrombin receptor antagonist, reduces cardiovascular death and recurrent thrombotic events when added to standard antiplatelet therapy in patients with stable atherosclerotic vascular disease.

OBJECTIVES The goal of this study was to test the hypothesis that treatment with vorapaxar reduces the rate of coronary stent thrombosis (ST) in stable patients with a history of coronary stenting.

METHODS TRA 2°P-TIMI 50 (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in

Patients With Atherosclerosis-Thrombolysis In Myocardial Infarction 50) was a multinational, randomized, double-blind, placebo-controlled trial of vorapaxar in stable patients with prior myocardial infarction, peripheral arterial disease, or stroke. We evaluated the rates of definite ST as adjudicated by a central events committee using Academic Research Consortium (ARC) criteria.

RESULTS A total of 26,449 patients were randomized, with 14,042 (53%) having a history of a coronary stent implantation before randomization, and an additional 449 patients receiving a coronary stent during the trial (total 14,491). During follow-up (median 2.5 years), there were 152 definite ST events, with the majority (92%) occurring late or very late. Vorapaxar reduced ARC definite ST (1.1% vs. 1.4%, hazard ratio [HR]: 0.71, 95% confidence interval [CI]: 0.51 to 0.98; $p = 0.037$). The reduction was consistent, regardless of time from percutaneous coronary intervention, history of diabetes, use of drug-eluting stents, and use of dual antiplatelet therapy (DAPT) at randomization. Vorapaxar increased GUSTO moderate/severe bleeding (HR: 1.57, 95% CI: 1.26 to 1.94; $p < 0.001$).

CONCLUSIONS The rate of ARC definite ST in stable patients, the majority of whom were receiving DAPT, was approximately 1.4% at 3 years. In stable patients with coronary stenting receiving standard antiplatelet therapy, vorapaxar administered for long-term secondary prevention significantly reduced ARC definite ST, including very late ST. (Trial to Assess the Effects of Vorapaxar [SCH 530348; MK-5348] in Preventing Heart Attack and Stroke in Patients With Atherosclerosis [TRA 2°P-TIMI 50] [P04737]; NCT00526474) (15).

Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy: The SECURITY Randomized Clinical Trial

A. Colombo, et al.

BACKGROUND The optimal duration of dual antiplatelet therapy (DAPT) following second-generation drug-eluting stent (DES) implantation is still debated.

OBJECTIVES The aim of this study was to test the noninferiority of 6 versus 12 months of DAPT in patients undergoing percutaneous coronary intervention with second-generation DES.

METHODS The SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trial was a 1:1 randomized, multicenter, international, investigator-driven, noninferiority study conducted from July 2009 to June 2014. Patients with a stable or unstable angina diagnosis or documented silent ischemia undergoing revascularization with at least 1 second-generation DES were eligible. The primary endpoint was a composite of cardiac death, myocardial infarction (MI), stroke, definite or probable stent thrombosis, or Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding at 12 months. The main secondary endpoint was a composite of cardiac death, MI, stroke, definite or probable stent thrombosis, or BARC type 2, 3, or 5 bleeding at 12 and 24 months.

RESULTS Overall, 1,399 patients were enrolled in the study and randomized to receive 6 months ($n = 682$) versus 12 months ($n = 717$) DAPT. The primary composite endpoint occurred, respectively, in 4.5% versus 3.7% (risk difference 0.8%; 95% confidence interval [CI]: −2.4% to 1.7%; $p = 0.469$) at 12 months. The upper 95% CI limit was lower than the pre-set margin of 2%, confirming the noninferiority hypothesis ($p < 0.05$). Moreover, no differences were observed in the occurrence of the secondary endpoint at 12 months (5.3% vs. 4.0%, difference: 1.2%; 95% CI: −1.0 to 3.4; $p = 0.273$) and between 12 and 24 months (1.5% vs. 2.2%, difference: −0.7%; 95% CI: −2.1 to 0.6; $p = 0.289$). Finally, no differences were observed in definite or probable stent thrombosis at 12 months (0.3% vs. 0.4%; difference: −0.1%; 95% CI: −0.7 to 0.4; $p = 0.694$) and between 12 and 24 months of follow-up (0.1% vs. 0%; difference: 0.1%; 95% CI: −0.1 to 0.4; $p = 0.305$).

CONCLUSIONS In a low-risk population, the noninferiority hypothesis of 6 vs. 12 months DAPT following second-generation DES implantation appears accepted for the incidence of cardiac death, MI, stroke, definite/probable stent thrombosis, and BARC type 3 or 5 bleeding at 12 months. (Second Generation Drug-Eluting Stent Implantation Followed by Six-Versus Twelve-Month Dual Antiplatelet Therapy; NCT00944333) (16).

Stent Thrombosis in New-Generation Drug-Eluting Stents in Patients With STEMI Undergoing Primary PCI: A Report From SCAAR

G. Sarno, et al.

BACKGROUND Some concerns still have not been resolved about the long-term safety of drug-eluting stents (DES) in patients with acute STEMI.

OBJECTIVES The aim of this study was to evaluate the stent thrombosis (ST) rate up to 3 years in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary percutaneous coronary intervention (PCI) with new-generation drug-eluting

stents (n-DES) compared with bare-metal stents (BMS) and old-generation drug-eluting stents (o-DES) enrolled in the SCAAR (Swedish Coronary Angiography and Angioplasty Registry).

METHODS From January 2007 to January 2013, 34,147 patients with STEMI were treated by PCI with n-DES (n = 4,811), o-DES (n = 4,271), or BMS (n = 25,065). The risks of early/late (up to 1 year) and very late definite ST (after 1 year) were estimated.

RESULTS Cox regression landmark analysis showed a significantly lower risk of early/late ST in patients treated with n-DES (hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0.43 to 0.99; p = 0.04) and o-DES (HR: 0.60; 95% CI: 0.41 to 0.89; p = 0.01) compared with the BMS group. The risk of very late ST was similar between the n-DES and BMS groups (HR: 1.52; 95% CI: 0.78 to 2.98; p = 0.21), whereas a higher risk of very late ST was observed with o-DES compared with BMS (HR: 2.88; 95% CI: 1.70 to 4.89; p < 0.01).

CONCLUSIONS Patients treated with n-DES have a lower risk of early/late ST than patients treated with BMS. The risk of very late ST is low and comparable between n-DES and BMS up to 3 years of follow-up, whereas o-DES treatment is associated with an increased risk of very late ST. The current STEMI guidelines might require an update in light of the results of this and other recent studies (17).

Clinical Outcomes With Bioabsorbable Polymer-Versus Durable Polymer-Based Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-Analysis

T. Palmerini, et al.

OBJECTIVES This study sought to investigate the relative safety and efficacy of bioabsorbable polymer (BP)-based biolimus-eluting stents (BES) versus durable-polymer (DP)-drug-eluting stents (DES) and bare-metal stents (BMS) by means of a network meta-analysis.

BACKGROUND Studies have suggested that BP-BES might reduce the risk of stent thrombosis (ST) and late adverse outcomes compared with first-generation DES. However, the relative safety and efficacy of BP-BES versus newer-generation DES coated with more biocompatible DP have not been investigated in depth.

METHODS Randomized controlled trials comparing BP-BES versus currently U.S.-approved DES or BMS were searched through MEDLINE, EMBASE, and Cochrane databases. Information on study design, inclusion and exclusion criteria, sample characteristics, and clinical outcomes was extracted.

RESULTS Data from 89 trials including 85,490 patients were analyzed. At 1-year follow-up, BP-BES were associated with lower rates of cardiac death/myocardial infarction (MI), MI, and target vessel revascularization (TVR) than BMS and lower rates of TVR than fast-release zotarolimus-eluting stents. The BP-BES had similar rates of cardiac death/MI, MI, and TVR compared with other second-generation DP-DES but higher rates of 1-year ST than cobalt-chromium everolimus-eluting stents (CoCr-EES). The BP-BES were associated with improved late outcomes compared with BMS and paclitaxel-eluting stents, considering the latest follow-up data available, with nonsignificantly different outcomes compared with other DP-DES although higher rates of definite ST compared with CoCr-EES.

CONCLUSIONS In this large-scale network meta-analysis, BP-BES were associated with superior clinical outcomes compared with BMS and first-generation DES and similar rates of cardiac death/MI, MI, and TVR compared with second-generation DP-DES but higher rates of definite ST than CoCr-EES (18).

Current Status of Bioresorbable Scaffolds in the Treatment of Coronary Artery Disease

J. Wiebe, et al.

State-of-the-art drug-eluting metal stents are the gold standard for interventional treatment of coronary artery disease. Although they overcome some disadvantages and limitations of plain balloon angioplasty and bare-metal stents, some limitations apply, most notably a chronic local inflammatory reaction due to permanent implantation of a foreign body, restriction of vascular vasomotion due to a metal cage, and the risk of late and very late stent thrombosis. The development of biodegradable scaffolds is a new approach that attempts to circumvent these drawbacks. These devices provide short-term scaffolding of the vessel and then dissolve, which should theoretically circumvent the side effects of metal drug-eluting stents. Various types of these bioresorbable scaffolds are currently under clinical evaluation. This review discusses different concepts of bioresorbable scaffolds with respect to material, design, and drug elution and presents the most recent evidence (19).

Long-Term Outcome of PCI Versus CABG in Insulin and Non–Insulin-Treated Diabetic Patients: Results From the FREEDOM Trial

G.D. Dangas, et al.

BACKGROUND The prospective, randomized FREEDOM (Comparison of Two Treatments for Multivessel Coronary

Artery Disease in Individuals With Diabetes) trial found coronary artery bypass graft surgery (CABG) was associated with better clinical outcomes than percutaneous coronary intervention (PCI) in patients with diabetes and multivessel disease, managed with or without insulin.

OBJECTIVES In this subgroup analysis of the FREEDOM trial, we examined the association of long-term clinical outcomes after revascularization in patients with insulin-treated diabetes mellitus (ITDM) compared with patients not treated with insulin.

METHODS A total of 1,850 FREEDOM subjects had an index revascularization procedure performed: 956 underwent PCI with drug-eluting stents (DES), and 894 underwent CABG. A total of 602 patients (32.5%) had ITDM (PCI/DES n = 325, 34%; CABG n = 277, 31%). Subjects were classified according to ITDM versus non-ITDM, with comparison of PCI/DES versus CABG for each group. Interaction analyses were performed for treatment by diabetes mellitus (DM) status alone and for treatment by DM status by coronary lesion complexity. Analyses were performed for the primary outcome composite of death/stroke/myocardial infarction (MI) using all available follow-up data.

RESULTS The overall 5-year event rate of death/stroke/MI was significantly higher in ITDM versus non-ITDM patients (28.7% vs. 19.5%, $p < 0.001$), which persisted even after adjustment for multiple baseline factors, angiographic complexity, and revascularization treatment group (death/stroke/MI hazard ratio [HR]: 1.35, 95% confidence interval [CI]: 1.06 to 1.73, $p = 0.014$). With respect to the primary composite endpoint, CABG was superior to PCI/DES in both DM types and the magnitude of treatment effect was similar (interaction $p = 0.40$) for ITDM (PCI vs. CABG HR: 1.21; 95% CI: 0.87 to 1.69) and non-ITDM patients (PCI vs. CABG HR: 1.46; 95% CI 1.10 to 1.94), even after adjusting for the angiographic SYNTAX score level. Based on 5-year event rates, the number needed to treat with CABG versus PCI to prevent 1 event is 12.7 in ITDM and 13.2 in non-ITDM.

CONCLUSIONS In patients with diabetes and multivessel coronary artery disease, the rate of major adverse cardiovascular events (death, MI, or stroke) is higher in patients treated with insulin than in those not treated with insulin. Furthermore, we did not detect a significant difference in the magnitude of PCI versus CABG treatment effect for patients treated with insulin and those not treated with insulin. (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes [FREEDOM]; NCT00086450) (20).

Long-Term Survival Following Coronary Artery Bypass Grafting: Off-Pump Versus On-Pump Strategies

J.B. Kim, et al.

OBJECTIVES This study sought to compare long-term survival after off- and on-pump coronary artery bypass grafting (CABG).

BACKGROUND Although several large-scale clinical trials have compared the surgical outcomes between off- and on-pump CABG, the long-term survival has not been compared between the 2 surgical strategies in a reasonably sized cohort.

METHODS We evaluated long-term survival data in 5,203 patients (age 62.9 ± 9.1 years, 1,340 females) who underwent elective isolated CABG (off-pump: n = 2,333; on-pump: n = 2,870) from 1989 through 2012. Vital statuses were validated using the Korean National Registry of Vital Statistics. Long-term survival was compared with the use of propensity scores and inverse probability weighting to adjust selection bias.

RESULTS Patients undergoing on-pump CABG had a higher number of distal anastomoses than those undergoing off-pump CABG (3.7 ± 1.2 vs. 3.0 ± 1.1; $p < 0.001$). Survival data were complete in 5,167 patients (99.3%), with a median follow-up duration of 6.4 years (interquartile range: 3.7 to 10.5 years; maximum 23.1 years). During follow-up, 1,181 patients (22.7%) died. After adjustment, both groups of patients showed a similar risk of death at 30 days (odds ratio: 0.70; 95% confidence interval [CI]: 0.35 to 1.40; $p = 0.31$) and up to 1 year (hazard ratio [HR]: 1.11; 95% CI: 0.74 to 1.65; $p = 0.62$). For overall mortality, however, patients undergoing off-pump CABG were at a significantly higher risk of death (HR: 1.43; 95% CI: 1.19 to 1.71; $p < 0.0001$) compared with those undergoing on-pump CABG. In subgroup analyses, on-pump CABG conferred survival benefits in most demographic, clinical, and anatomic subgroups compared with off-pump CABG.

CONCLUSIONS In patients undergoing elective isolated CABG, on-pump strategy conferred a long-term survival advantage compared with off-pump strategy (21).

Drug-Eluting Balloon Versus Standard Balloon Angioplasty for Infrapopliteal Arterial Revascularization in Critical Limb Ischemia: 12-Month Results From the IN.PACT DEEP Randomized Trial

T. Zeller, et al.

BACKGROUND Drug-eluting balloons (DEB) may reduce infrapopliteal restenosis and reintervention

rates versus percutaneous transluminal angioplasty (PTA) and improve wound healing/limb preservation.

OBJECTIVES The goal of this clinical trial was to assess the efficacy and safety of IN.PACT Amphirion drug-eluting balloons (IA-DEB) compared to PTA for infrapopliteal arterial revascularization in patients with critical limb ischemia (CLI).

METHODS Within a prospective, multicenter, randomized, controlled trial with independent clinical event adjudication and angiographic and wound core laboratories 358 CLI patients were randomized 2:1 to IA-DEB or PTA. The 2 coprimary efficacy endpoints through 12 months were clinically driven target lesion revascularization (CD-TLR) and late lumen loss (LLL). The primary safety endpoint through 6 months was a composite of all-cause mortality, major amputation, and CD-TLR.

RESULTS Clinical characteristics were similar between the 2 groups. Significant baseline differences between the IA-DEB and PTA arms included mean lesion length (10.2 cm vs. 12.9 cm; $p = 0.002$), impaired inflow (40.7% vs. 28.8%; $p = 0.035$), and previous target limb revascularization (32.2% vs. 21.8%; $p = 0.047$). Primary efficacy results of IA-DEB versus PTA were CD-TLR of 9.2% versus 13.1% ($p = 0.291$) and LLL of 0.61 ± 0.78 mm versus 0.62 ± 0.78 mm ($p = 0.950$). Primary safety endpoints were 17.7% versus 15.8% ($p = 0.021$) and met the noninferiority hypothesis. A safety signal driven by major amputations through 12 months was observed in the IA-DEB arm versus the PTA arm (8.8% vs. 3.6%; $p = 0.080$).

CONCLUSIONS In patients with CLI, IA-DEB had comparable efficacy to PTA. While primary safety was met, there was a trend towards an increased major amputation rate through 12 months compared to PTA. (Study of IN.PACT Amphirion™ Drug Eluting Balloon vs. Standard PTA for the Treatment of Below the Knee Critical Limb Ischemia [INPACT-DEEP]; NCT00941733) (22).

Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by Optical Coherence Tomography: The EASY-FIT Study

K. Komukai, et al.

BACKGROUND The detailed mechanism of plaque stabilization by statin therapy is not fully understood.

OBJECTIVES The aim of this study was to assess the effect of lipid-lowering therapy with 20 mg/day of atorvastatin versus 5 mg/day of atorvastatin on fibrous cap thickness in coronary atherosclerotic plaques by using optical coherence tomography (OCT).

METHODS Seventy patients with unstable angina pectoris and untreated dyslipidemia were randomized to either 20 mg/day or 5 mg/day of atorvastatin therapy. OCT was performed to assess intermediate nonculprit lesions at baseline and 12-month follow-up.

RESULTS Serum low-density lipoprotein cholesterol level was significantly lower during therapy with 20 mg/day compared with 5 mg/day of atorvastatin (69 mg/dl vs. 78 mg/dl; $p = 0.039$). The increase in fibrous cap thickness was significantly greater with 20 mg/day compared with 5 mg/day of atorvastatin (69% vs. 17%; $p < 0.001$). The increase in fibrous cap thickness correlated with the decrease in serum levels of low-density lipoprotein cholesterol ($R = -0.450$; $p < 0.001$), malondialdehyde-modified low-density lipoprotein ($R = -0.283$; $p = 0.029$), high-sensitivity C-reactive protein ($R = -0.276$; $p = 0.033$), and matrix metalloproteinase-9 ($R = -0.502$; $p < 0.001$), and the decrease in grade of OCT-derived macrophages ($R = -0.415$; $p = 0.003$).

CONCLUSIONS Atorvastatin therapy at 20 mg/day provided a greater increase in fibrous cap thickness in coronary plaques compared with 5 mg/day of atorvastatin. The increase of fibrous cap was associated with the decrease in serum atherogenic lipoproteins and inflammatory biomarkers during atorvastatin therapy. (Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by Optical Coherence Tomography: The EASY-FIT Study; NCT00700037) (23).

GENETICS, OMICS, & TISSUE REGENERATION

Targeted Next-Generation Sequencing Identifies Pathogenic Variants in Familial Congenital Heart Disease

G.M. Blue, et al.

BACKGROUND Many genes have been implicated in the development of congenital heart disease (CHD). Next-generation sequencing offers opportunities for genetic testing but is often complicated by logistic and interpretative hurdles.

OBJECTIVES This study sought to apply next-generation sequencing technology to CHD families with multiple affected members using a purpose-designed gene panel to assess diagnostic potential for future clinical applications.

METHODS We designed a targeted next-generation sequencing gene panel for 57 genes previously implicated in CHD. Probands were screened in 16 families with strong CHD histories and in 15 control subjects. Variants affecting protein-coding regions were classified in silico using prediction programs and filtered according to predicted mode of inheritance, minor allele frequencies, and presence in databases such as dbSNP (Single Nucleotide Polymorphism Database) and ESP (Exome Sequencing Project). Disease segregation studies were conducted in variants identified in CHD cases predicted to be deleterious and with minor allele frequencies <0.1%.

RESULTS Thirteen potential disease-causing variants were identified in 9 families. Of these, 5 variants segregated with disease phenotype, revealing a likely molecular diagnosis in 31% of this cohort. Significant increases in the number of "indels, nonsense, and splice" variants, as well as variants classified as "probably damaging" were identified in CHD cases but not in control subjects. Also, there was a significant increase in the total number of "rare" and "low" frequency variants (minor allele frequencies <0.05) in the CHD cases.

CONCLUSIONS When multiple relatives are affected by CHD, a gene panel–based approach may identify its cause in up to 31% of families. Identifying causal variants has implications for clinical care and future family planning (24).

A Roadmap to Investigate the Genetic Basis of Bicuspid Aortic Valve and its Complications: Insights From the International BAVCon (Bicuspid Aortic Valve Consortium)

S.K. Prakash, et al.

Bicuspid aortic valve (BAV) is the most common adult congenital heart defect and is found in 0.5% to 2.0% of the general population. The term "BAV" refers to a heterogeneous group of disorders characterized by diverse aortic valve malformations with associated aortopathy, congenital heart defects, and genetic syndromes. Even after decades of investigation, the genetic determinants of BAV and its complications remain largely undefined. Just as BAV phenotypes are highly variable, the genetic etiologies of BAV are equally diverse and vary from complex inheritance in families to sporadic cases without any evidence of inheritance. In this paper, the authors discuss current concepts in BAV genetics and propose a roadmap for unraveling unanswered questions about BAV through the integrated analysis of genetic and clinical data (25).

Yield of Serial Evaluation in At-Risk Family Members of Patients With ARVD/C

A.S.J.M. te Riele, et al.

BACKGROUND Incomplete penetrance and variable expressivity of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) complicate family screening.

OBJECTIVES The objective of the present study was to determine the optimal approach to longitudinal follow-up regarding: 1) screening interval; and 2) testing strategy in at-risk relatives of ARVD/C patients.

METHODS We included 117 relatives (45% male, age 33.3 ± 16.3 years) from 64 families who were at risk of developing ARVD/C by virtue of their familial predisposition (72% mutation carriers [92% plakophilin-2]; 28% first-degree relatives of a mutation-negative proband). Subjects were evaluated by electrocardiography (ECG), Holter monitoring, signal-averaged ECG, and cardiac magnetic resonance (CMR). Disease progression was defined as the development of a new criterion by the 2010 Task Force Criteria (not the "Hamid criteria") at last follow-up that was absent at enrollment.

RESULTS At first evaluation, 43 subjects (37%) fulfilled an ARVD/C diagnosis according to the 2010 Task Force Criteria. Among the remaining 74 subjects (63%), 11 of 37 (30%) with complete re-evaluation experienced disease progression during 4.1 ± 2.3 years of follow-up. Electrical progression (n = 10 [27%], including by ECG [14%], Holter monitoring [11%], or signal-averaged ECG [14%]) was more frequently observed than structural progression (n = 1 [3%] on CMR). All 5 patients (14%) with clinical ARVD/C diagnosis at last follow-up had an abnormal ECG or Holter monitor recording, and the only patient with an abnormal CMR already had an abnormal ECG at enrollment.

CONCLUSIONS Over a mean follow-up of 4 years, our study showed that: 1) almost one-third of at-risk relatives have electrical progression; 2) structural progression is rare; and 3) electrical abnormalities precede detectable structural changes. This information could be valuable in determining family screening protocols (26).

Mutations in *SCN10A* Are Responsible for a Large Fraction of Cases of Brugada Syndrome

D. Hu, et al.

BACKGROUND BrS is an inherited sudden cardiac death syndrome. Less than 35% of BrS probands have genetically identified pathogenic variants. Recent

evidence has implicated *SCN10A*, a neuronal sodium channel gene encoding $Na_v1.8$, in the electrical function of the heart.

OBJECTIVES The purpose of this study was to test the hypothesis that *SCN10A* variants contribute to the development of Brugada syndrome (BrS).

METHODS Clinical analysis and direct sequencing of BrS susceptibility genes were performed for 150 probands and family members as well as >200 healthy controls. Expression and coimmunoprecipitation studies were performed to functionally characterize the putative pathogenic mutations.

RESULTS We identified 17 *SCN10A* mutations in 25 probands (20 male and 5 female); 23 of the 25 probands (92.0%) displayed overlapping phenotypes. *SCN10A* mutations were found in 16.7% of BrS probands, approaching our yield for *SCN5A* mutations (20.1%). Patients with BrS who had *SCN10A* mutations were more symptomatic and displayed significantly longer PR and QRS intervals compared with *SCN10A*-negative BrS probands. The majority of mutations localized to the transmembrane-spanning regions. Heterologous coexpression of wild-type (WT) *SCN10A* with WT-*SCN5A* in HEK cells caused a near doubling of sodium channel current compared with WT-*SCN5A* alone. In contrast, coexpression of *SCN10A* mutants (R14L and R1268Q) with WT-*SCN5A* caused a 79.4% and 84.4% reduction in sodium channel current, respectively. The coimmunoprecipitation studies provided evidence for the coassociation of $Na_v1.8$ and $Na_v1.5$ in the plasma membrane.

CONCLUSIONS Our study identified *SCN10A* as a major susceptibility gene for BrS, thus greatly enhancing our ability to genotype and risk stratify probands and family members (27).

HCN4 Mutations in Multiple Families With Bradycardia and Left Ventricular Noncompaction Cardiomyopathy

A. Milano, et al.

BACKGROUND Familial forms of primary sinus bradycardia have sometimes been attributed to mutations in *HCN4*, *SCN5A*, and *ANK2*. In these studies, no structural cardiac alterations were reported in mutation carriers. However, a cluster of reports in the literature describe patients presenting with sinus bradycardia in association with left ventricular noncompaction cardiomyopathy (LVNC), pointing to a shared genetic cause.

OBJECTIVES This study sought to identify the genetic defect underlying the combined clinical presentation of bradycardia and LVNC, hypothesizing that these 2 clinical abnormalities have a common genetic cause.

METHODS Exome sequencing was carried out in 2 cousins from the index family that were affected by the combined bradycardia-LVNC phenotype; shared variants thus identified were subsequently overlaid with the chromosomal regions shared among 5 affected family members that were identified using single nucleotide polymorphism array analysis.

RESULTS The combined linkage analysis and exome sequencing in the index family identified 11 novel variants shared among the 2 affected cousins. One of these, p.Gly482Arg in HCN4, segregated with the combined bradycardia and LVNC phenotype in the entire family. Subsequent screening of *HCN4* in 3 additional families with the same clinical combination of bradycardia and LVNC identified *HCN4* mutations in each. In electrophysiological studies, all found *HCN4* mutations showed a more negative voltage dependence of activation, consistent with the observed bradycardia.

CONCLUSIONS Although mutations in *HCN4* have been previously linked to bradycardia, our study provides the first evidence to our knowledge that mutations in this ion channel gene also may be associated with structural abnormalities of the myocardium (28).

microRNAs in Cardiovascular Diseases: Current Knowledge and the Road Ahead

G. Condorelli, et al.

Over the last few years, the field of microribonucleic acid (miRNA) in cardiovascular biology and disease has expanded at an incredible pace. miRNAs are themselves part of a larger family, that of non-coding RNAs, the importance of which for biological processes is starting to emerge. miRNAs are ~22-nucleotide-long RNA sequences that can legate messenger (m)RNAs at partially complementary binding sites, and hence regulate the rate of protein synthesis by altering the stability of the targeted mRNAs. In the cardiovascular system, miRNAs have been shown to be critical regulators of development and physiology. They control basic functions in virtually all cell types relevant to the cardiovascular system (such as endothelial cells, cardiac muscle, smooth muscle, inflammatory cells, and fibroblasts) and, thus, are directly involved in the pathophysiology of many cardiovascular diseases. As a result of their role in disease, they are being studied for exploitation in diagnostics, prognostics, and therapeutics. However,

there are still significant obstacles that need to be overcome before they enter the clinical arena. We present here a review of the literature and outline the directions toward their use in the clinic (29).

Circulating miR-29a, Among Other Up-Regulated MicroRNAs, Is the Only Biomarker for Both Hypertrophy and Fibrosis in Patients With Hypertrophic Cardiomyopathy

R. Roncarati, et al.

OBJECTIVES The purpose of this paper was to determine whether microRNAs (miRNAs) involved in myocardial remodeling were differentially expressed in the blood of hypertrophic cardiomyopathy (HCM) patients, and whether circulating miRNAs correlated with the degree of left ventricular hypertrophy and fibrosis.

BACKGROUND miRNAs—small, noncoding ribonucleic acids (RNAs) that regulate gene expression by inhibiting RNA translation—modulate cellular function. Myocardial miRNAs modulate processes such as cardiomyocyte (CM) hypertrophy, excitation-contraction coupling, and apoptosis; non-CM-specific miRNAs regulate myocardial vascularization and fibrosis. Recently, the possibility that circulating miRNAs may be biomarkers of cardiovascular disease has been raised.

METHODS Forty-one HCM patients were characterized with conventional transthoracic echocardiography and cardiac magnetic resonance. Peripheral plasma levels of 21 miRNAs were assessed by quantitative real-time polymerase chain reaction and were compared with levels in a control group of 41 age- and sex-matched blood donors.

RESULTS Twelve miRNAs (miR-27a, -199a-5p, -26a, -145, -133a, -143, -199a-3p, -126-3p, -29a, -155, -30a, and -21) were significantly increased in HCM plasma. However, only 3 miRNAs (miR-199a-5p, -27a, and -29a) correlated with hypertrophy; more importantly, only miR-29a correlated also with fibrosis.

CONCLUSIONS Our data suggest that cardiac remodeling associated with HCM determines a significant release of miRNAs into the bloodstream: the circulating levels of both cardiac- and non-cardiac-specific miRNAs are significantly increased in the plasma of HCM patients. However, correlation with left ventricular hypertrophy parameters holds true for only a few miRNAs (i.e, miR-199a-5p, -27a, and -29a), whereas only miR-29a is significantly associated with both hypertrophy and fibrosis, identifying it as a potential biomarker for myocardial remodeling assessment in HCM (30).

Novel Genetic Markers Associate With Atrial Fibrillation Risk in Europeans and Japanese

S.A. Lubitz, et al.

OBJECTIVES This study sought to identify nonredundant atrial fibrillation (AF) genetic susceptibility signals and examine their cumulative relations with AF risk.

BACKGROUND AF-associated loci span broad genomic regions that may contain multiple susceptibility signals. Whether multiple signals exist at AF loci has not been systematically explored.

METHODS We performed association testing conditioned on the most significant, independently associated genetic markers at 9 established AF loci using 2 complementary techniques in 64,683 individuals of European ancestry (3,869 incident and 3,302 prevalent AF cases). Genetic risk scores were created and tested for association with AF in Europeans and an independent sample of 11,309 individuals of Japanese ancestry (7,916 prevalent AF cases).

RESULTS We observed at least 4 distinct AF susceptibility signals on chromosome 4q25 upstream of *PITX2*, but not at the remaining 8 AF loci. A multilocus score comprised 12 genetic markers demonstrated an estimated 5-fold gradient in AF risk. We observed a similar spectrum of risk associated with these markers in Japanese. Regions containing AF signals on chromosome 4q25 displayed a greater degree of evolutionary conservation than the remainder of the locus, suggesting that they may tag regulatory elements.

CONCLUSIONS The chromosome 4q25 AF locus is architecturally complex and harbors at least 4 AF susceptibility signals in individuals of European ancestry. Similar polygenic AF susceptibility exists between Europeans and Japanese. Future work is necessary to identify causal variants, determine mechanisms by which associated loci predispose to AF, and explore whether AF susceptibility signals classify individuals at risk for AF and related morbidity (31).

Induced Pluripotent Stem Cells for the Study of Cardiovascular Disease

J.J. Savla, et al.

Groundbreaking advances in stem cell research have led to techniques for the creation of human cardiomyocytes from cells procured from a variety of sources, including a simple skin biopsy. Since the advent of this technology, most research has focused on utilizing these cells for therapeutic purposes. However, recent studies have demonstrated that stem

cell-derived cardiomyocytes generated from patients with inherited cardiovascular disorders recapitulate key phenotypic features of disease in vitro. Furthermore, these cells can be maintained in culture for prolonged periods of time and used for extensive biochemical and physiological analysis. By serving as models of inherited cardiac disorders, these systems have the potential to fundamentally change the manner in which cardiovascular disease is studied and new therapies are developed (32).

Intracoronary Cardiosphere-Derived Cells After Myocardial Infarction: Evidence of Therapeutic Regeneration in the Final 1-Year Results of the CADUCEUS Trial (CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction)

K. Malliaras, et al.

OBJECTIVES This study sought to report full 1-year results, detailed magnetic resonance imaging analysis, and determinants of efficacy in the prospective, randomized, controlled CADUCEUS (CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction) trial.

BACKGROUND Cardiosphere-derived cells (CDCs) exerted regenerative effects at 6 months in the CADUCEUS trial. Complete results at the final 1-year endpoint are unknown.

METHODS Autologous CDCs (12.5 to 25 $\times$ 10^6) grown from endomyocardial biopsy specimens were infused via the intracoronary route in 17 patients with left ventricular dysfunction 1.5 to 3 months after myocardial infarction (MI) (plus 1 infused off-protocol 14 months post-MI). Eight patients were followed as routine-care control patients.

RESULTS In 13.4 months of follow-up, safety endpoints were equivalent between groups. At 1 year, magnetic resonance imaging revealed that CDC-treated patients had smaller scar size compared with control patients. Scar mass decreased and viable mass increased in CDC-treated patients but not in control patients. The single patient infused 14 months post-MI responded similarly. CDC therapy led to improved regional function of infarcted segments compared with control patients. Scar shrinkage correlated with an increase in viability and with improvement in regional function. Scar reduction correlated with baseline scar size but not with a history of temporally remote MI or time from MI to infusion. The changes in left ventricular ejection fraction in CDC-treated subjects were consistent with the natural relationship between scar size and ejection fraction post-MI.

CONCLUSIONS Intracoronary administration of autologous CDCs did not raise significant safety concerns. Preliminary indications of bioactivity include decreased scar size, increased viable myocardium, and improved regional function of infarcted myocardium at 1 year post-treatment. These results, which are consistent with therapeutic regeneration, merit further investigation in future trials. (CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction [CADUCEUS]; NCT00893360) (33).

Cultured Human Bone Marrow–Derived CD31$^+$ Cells Are Effective for Cardiac and Vascular Repair Through Enhanced Angiogenic, Adhesion, and Anti-Inflammatory Effects

S.-W. Kim, et al.

BACKGROUND Cell therapy for cardiovascular disease has been limited by low engraftment of administered cells and modest therapeutic effects. Bone marrow (BM) -derived CD31$^+$ cells are a promising cell source owing to their high angiovasculogenic and paracrine activities.

OBJECTIVES This study sought to identify culture conditions that could augment the cell adhesion, angiogenic, and anti-inflammatory activities of BM-derived CD31$^+$ cells, and to determine whether these cultured CD31$^+$ cells are effective for cardiac and vascular repair.

METHODS CD31$^+$ cells were isolated from human BM by magnetic-activated cell sorting and cultured for 10 days under hematopoietic stem cell, mesenchymal stem cell, or endothelial cell culture conditions. These cells were characterized by adhesion, angiogenesis, and inflammatory assays. The best of the cultured cells were implanted into myocardial infarction (MI) and hindlimb ischemia (HLI) models to determine therapeutic effects and underlying mechanisms.

RESULTS The CD31$^+$ cells cultured in endothelial cell medium (EC-CD31$^+$ cells) showed the highest adhesion and angiogenic activities and lowest inflammatory properties in vitro compared with uncultured or other cultured CD31$^+$ cells. When implanted into mouse MI or HLI models, EC-CD31$^+$ cells improved cardiac function and repaired limb ischemia to a greater extent than uncultured CD31$^+$ cells. Histologically, injected EC-CD31$^+$ cells exhibited higher retention, neovascularization, and cardiomyocyte proliferation. Importantly, cell retention and endothelial transdifferentiation was sustained up to 1 year.

CONCLUSIONS Short-term cultured EC-CD31$^+$ cells have higher cell engraftment, vessel-formation,

cardiomyocyte proliferation, and anti-inflammatory potential, are highly effective for both cardiac and peripheral vascular repair, and enhance survival of mice with heart failure. These cultured $CD31^+$ cells may be a promising source for treating ischemic cardiovascular diseases (34).

Translating Stem Cell Research to Cardiac Disease Therapies: Pitfalls and Prospects for Improvement

M.R. Rosen, et al.

Over the past 2 decades, there have been numerous stem cell studies focused on cardiac diseases, ranging from proof-of-concept to phase 2 trials. This series of papers focuses on the legacy of these studies and the outlook for future treatment of cardiac diseases with stem cell therapies. The first section by Drs. Rosen and Myerburg is an independent review that analyzes the basic science and translational strategies supporting the rapid advance of stem cell technology to the clinic, the philosophies behind them, trial designs, and means for going forward that may impact favorably on progress. The second and third sections were collected as responses to the initial section of this review. The commentary by Drs. Francis and Cole discusses the review by Drs. Rosen and Myerburg and details how trial outcomes can be affected by noise, poor trial design (particularly the absence of blinding), and normal human tendencies toward optimism and denial. The final, independent paper by Dr. Marbán takes a different perspective concerning the potential for positive impact of stem cell research applied to heart disease and future prospects for its clinical application. *(Compiled by the JACC editors)* (35).

Effect of Human Donor Cell Source on Differentiation and Function of Cardiac Induced Pluripotent Stem Cells

V. Sanchez-Freire, et al.

BACKGROUND Human-induced pluripotent stem cells (iPSCs) are a potentially unlimited source for generation of cardiomyocytes (iPSC-CMs). However, current protocols for iPSC-CM derivation face several challenges, including variability in somatic cell sources and inconsistencies in cardiac differentiation efficiency.

OBJECTIVES This study aimed to assess the effect of epigenetic memory on differentiation and function of iPSC-CMs generated from somatic cell sources of cardiac versus noncardiac origins.

METHODS Cardiac progenitor cells (CPCs) and skin fibroblasts from the same donors were reprogrammed into iPSCs and differentiated into iPSC-CMs via embryoid body and monolayer-based differentiation protocols.

RESULTS Differentiation efficiency was found to be higher in CPC-derived iPSC-CMs (CPC-iPSC-CMs) than in fibroblast-derived iPSC-CMs (Fib-iPSC-CMs). Gene expression analysis during cardiac differentiation demonstrated up-regulation of cardiac transcription factors in CPC-iPSC-CMs, including *NKX2-5*, *MESP1*, *ISL1*, *HAND2*, *MYOCD*, *MEF2C*, and *GATA4*. Epigenetic assessment revealed higher methylation in the promoter region of *NKX2-5* in Fib-iPSC-CMs compared with CPC-iPSC-CMs. Epigenetic differences were found to dissipate with increased cell passaging, and a battery of in vitro assays revealed no significant differences in their morphological and electrophysiological properties at early passage. Finally, cell delivery into a small animal myocardial infarction model indicated that CPC-iPSC-CMs and Fib-iPSC-CMs possess comparable therapeutic capabilities in improving functional recovery in vivo.

CONCLUSIONS This is the first study to compare differentiation of iPSC-CMs from human CPCs versus human fibroblasts from the same donors. The authors demonstrate that although epigenetic memory improves differentiation efficiency of cardiac versus noncardiac somatic cell sources in vitro, it does not contribute to improved functional outcome in vivo (36).

The Role of Monocytes in Angiogenesis and Atherosclerosis

A.S. Jaipersad, et al.

New vessel formation inside the arterial wall and atherosclerotic plaques plays a critical role in pathogenesis of heart attacks and strokes. The 2 known mechanisms resulting in the formation of new vessels within the plaque are local ischemia and inflammation. Blood monocytes play an important role in both processes. First, they express receptors for vascular endothelial growth factor and some of them may serve as circulating ancestors of endothelial cells. Second, monocytes are associated with inflammation by synthesis of inflammatory molecules following their activation (e.g., after stimulation of Toll-like receptors). Neovascularization is a reparative response to ischemia, and includes 3 processes: angiogenesis, arteriogenesis, and vasculogenesis. Angiogenesis, the formation of new capillary vessels is known to occur in response to a hypoxic environment. The interaction

between leukocytes and vascular wall via overexpression of various molecules facilitates the migration of inflammatory cells into the plaque microenvironment. Monocytes are intimately involved in tissue damage and repair and an imbalance of these processes may have detrimental consequences for plaque development and stability. Importantly, monocytes are comprised of distinct subsets with different cell surface markers and functional characteristics and this heterogeneity may be relevant to angiogenic processes in atherosclerosis. The aim of this review article is to present an overview of the available evidence supporting a role for monocytes in angiogenesis and atherosclerosis (37).

CV PREVENTION & HEALTH PROMOTION

Sports and Exercise Cardiology in the United States: Cardiovascular Specialists as Members of the Athlete Healthcare Team

C.E. Lawless, et al.

In recent years, athletic participation has more than doubled in all major demographic groups, while simultaneously, children and adults with established heart disease desire participation in sports and exercise. Despite conferring favorable long-term effects on well-being and survival, exercise can be associated with risk of adverse events in the short term. Complex individual cardiovascular (CV) demands and adaptations imposed by exercise present distinct challenges to the cardiologist asked to evaluate athletes. Here, we describe the evolution of sports and exercise cardiology as a unique discipline within the continuum of CV specialties, provide the rationale for tailoring of CV care to athletes and exercising individuals, define the role of the CV specialist within the athlete care team, and lay the foundation for the development of Sports and Exercise Cardiology in the United States. In 2011, the American College of Cardiology launched the Section of Sports and Exercise Cardiology. Membership has grown from 150 to over 4,000 members in just 2 short years, indicating marked interest from the CV community to advance the integration of sports and exercise cardiology into mainstream CV care. Although the current athlete CV care model has distinct limitations, here, we have outlined a new paradigm of care for the American athlete and exercising individual. By practicing and promoting this new paradigm, we believe we will enhance the CV care of athletes of all ages, and serve the greater athletic community and our nation as a whole, by allowing safest participation in sports and physical activity for all individuals who seek this lifestyle (38).

Leisure-Time Running Reduces All-Cause and Cardiovascular Mortality Risk

D.-C. Lee, et al.

BACKGROUND Although running is a popular leisure-time physical activity, little is known about the long-term effects of running on mortality. The dose-response relations between running, as well as the change in running behaviors over time, and mortality remain uncertain.

OBJECTIVES We examined the associations of running with all-cause and cardiovascular mortality risks in 55,137 adults, 18 to 100 years of age (mean age 44 years).

METHODS Running was assessed on a medical history questionnaire by leisure-time activity.

RESULTS During a mean follow-up of 15 years, 3,413 all-cause and 1,217 cardiovascular deaths occurred. Approximately 24% of adults participated in running in this population. Compared with nonrunners, runners had 30% and 45% lower adjusted risks of all-cause and cardiovascular mortality, respectively, with a 3-year life expectancy benefit. In dose-response analyses, the mortality benefits in runners were similar across quintiles of running time, distance, frequency, amount, and speed, compared with nonrunners. Weekly running even <51 min, <6 miles, 1 to 2 times, <506 metabolic equivalent-minutes, or <6 miles/h was sufficient to reduce risk of mortality, compared with not running. In the analyses of change in running behaviors and mortality, persistent runners had the most significant benefits, with 29% and 50% lower risks of all-cause and cardiovascular mortality, respectively, compared with never-runners.

CONCLUSIONS Running, even 5 to 10 min/day and at slow speeds <6 miles/h, is associated with markedly reduced risks of death from all causes and cardiovascular disease. This study may motivate healthy but sedentary individuals to begin and continue running for substantial and attainable mortality benefits (39).

A Systematic Examination of the 2013 ACC/AHA Pooled Cohort Risk Assessment Tool for Atherosclerotic Cardiovascular Disease

K.N. Karmali, et al.

BACKGROUND The 2013 American College of Cardiology/American Heart Association updated cholesterol guidelines recommend the use of Pooled Cohort Equations to estimate 10-year absolute risk for atherosclerotic cardiovascular disease (ASCVD) in primary prevention.

OBJECTIVES This study sought to systematically examine the Pooled Cohort Equations to determine risk factor levels required to exceed risk thresholds outlined in new cholesterol guidelines.

METHODS We entered continuous risk factor levels in isolation and in specified combinations with the risk tool, and we observed predicted risk output patterns. We used the 10-year ASCVD risk threshold of ≥7.5% as a clinically relevant risk threshold.

RESULTS We demonstrated that a hypothetical man or woman can reach clinically relevant risk thresholds throughout the eligible age spectrum of 40 to 79 years of age, depending on the associated risk factor burden in all race-sex groups. Age continues to be a major determinant of 10-year ASCVD risk for both men and women. Compared with the previous risk assessment tool used in cholesterol guidelines, the inclusion of a stroke endpoint and use of race-specific coefficients permit identification of at-risk African Americans and non-Hispanic white women at much younger ages and lower risk factor levels.

CONCLUSIONS These data provide context of specific risk factor levels and groups of individuals who are likely to have 10-year ASCVD risk estimates ≥7.5%. Age continues to be a major driver of risk, which highlights the importance of the clinician-patient discussion before statin therapy is initiated (40).

Low-Risk Diet and Lifestyle Habits in the Primary Prevention of Myocardial Infarction in Men: A Population-Based Prospective Cohort Study

A. Åkesson, et al.

BACKGROUND Adherence to a combination of healthy dietary and lifestyle practices may have an impressive impact on the primary prevention of myocardial infarction (MI).

OBJECTIVES The aim of this study was to examine the benefit of combined low-risk diet and healthy lifestyle practices on the incidence of MI in men.

METHODS The population-based, prospective cohort of Swedish men comprised 45- to 79-year-old men who completed a detailed questionnaire on diet and lifestyle at baseline in 1997. In total, 20,721 men with no history of cancer, cardiovascular disease, diabetes, hypertension, or high cholesterol levels were followed through 2009. Low-risk behavior included 5 factors: a healthy diet (top quintile of Recommended Food Score), moderate alcohol consumption (10 to 30 g/day), no smoking, being physically active (walking/bicycling ≥40 min/day and exercising ≥1 h/week), and having no abdominal adiposity (waist circumference <95 cm).

RESULTS During 11 years of follow-up, we ascertained 1,361 incident cases of MI. The low-risk dietary choice together with moderate alcohol consumption was associated with a relative risk of 0.65 (95% confidence interval [CI]: 0.48 to 0.87) compared with men having 0 of 5 low-risk factors. Men having all 5 low-risk factors compared with those with 0 low-risk factors had a relative risk of 0.14 (95% CI: 0.04 to 0.43). This combination of healthy behaviors, present in 1% of the men, could prevent 79% (95% CI: 34% to 93%) of the MI events on the basis of the study population.

CONCLUSIONS Almost 4 of 5 MIs in men may be preventable with a combined low-risk behavior (41).

Impact of Long-Term Burden of Excessive Adiposity and Elevated Blood Pressure From Childhood on Adulthood Left Ventricular Remodeling Patterns: The Bogalusa Heart Study

C.-C. Lai, et al.

BACKGROUND Cardiovascular risk factors are associated with left ventricular hypertrophy (LVH), but little is known regarding related impact of longitudinal measures of childhood adiposity and LV hemodynamic variables.

OBJECTIVES The aim of this study was to examine the impact of cumulative long-term burden and trends of excessive adiposity and elevated blood pressure (BP) during childhood on adulthood LVH and LV geometric remodeling patterns.

METHODS This longitudinal study consisted of 1,061 adults, age 24 to 46 years, who had been examined 4 or more times for body mass index (BMI) and BP starting in childhood, with a mean follow-up of 28.0 years. The area under the curve (AUC) was calculated as a measure of long-term burden (total AUC) and trends (incremental AUC) of BMI and BP from childhood to adulthood. Four LV geometric types were defined—normal, concentric remodeling (CR), eccentric hypertrophy (EH), and concentric hypertrophy (CH)—all on the basis of LV mass indexed for body height ($m^{2.7}$) and relative wall thickness.

RESULTS Higher values of BMI and systolic and diastolic BP in childhood and adulthood, as well as total AUC and incremental AUC, were all significantly associated with higher LV mass index and LVH, adjusted for race, sex, and age. In addition, higher values of BMI and BP in childhood and adulthood,

total AUC, and incremental AUC were significantly associated with EH and CH but not with CR. Importantly, all of these measures of BMI had a consistently and significantly greater influence on EH than did measures of BP.

CONCLUSIONS These findings indicate that the adverse influence of excessive adiposity and elevated BP levels on LVH begins in childhood (42).

Aspirin Therapy in Primary Cardiovascular Disease Prevention: A Position Paper of the European Society of Cardiology Working Group on Thrombosis

S. Halvorsen, et al.

Although the use of oral anticoagulants (vitamin K antagonists) has been abandoned in primary cardiovascular prevention due to lack of a favorable benefit-to-risk ratio, the indications for aspirin use in this setting continue to be a source of major debate, with major international guidelines providing conflicting recommendations. Here, we review the evidence in favor and against aspirin therapy in primary prevention based on the evidence accumulated so far, including recent data linking aspirin with cancer protection. While awaiting the results of several ongoing studies, we argue for a pragmatic approach to using low-dose aspirin in primary cardiovascular prevention and suggest its use in patients at high cardiovascular risk, defined as ≥2 major cardiovascular events (death, myocardial infarction, or stroke) projected per 100 person-years, who are not at increased risk of bleeding (43).

Spironolactone Reduces Cardiovascular and Cerebrovascular Morbidity and Mortality in Hemodialysis Patients

Y. Matsumoto, et al.

OBJECTIVES This study sought to assess whether spironolactone treatment reduces the high incidence of cardiovascular and cerebrovascular (CCV) morbidity and mortality in hemodialysis (HD) patients.

BACKGROUND Aldosterone receptor blockers reduce cardiac-related events, but the efficacy of the agents in HD patients is unclear.

METHODS A 3-year randomized trial involving 5 clinics was performed. Of the 309 oligoanuric HD patients enrolled in the study, 157 patients were randomly assigned to receive 25 mg/day of spironolactone without any restriction on dietary potassium intake (treatment group), and 152 patients were assigned to a control group. The primary outcome was a composite of death from CCV events or hospitalization for CCV events, and the secondary outcome was death from all causes.

RESULTS During the 3-year follow-up, the primary outcome occurred in 5.7% of patients in the treatment group and in 12.5% of patients in the control group. Hazard ratios (HRs) for the primary outcome for treatment were 0.404 (95% confidence interval [CI]: 0.202 to 0.809; $p = 0.017$) and 0.379 (95% CI: 0.173 to 0.832; $p = 0.016$) before and after adjustment, respectively. The secondary outcome was significantly reduced in the treatment group compared with the control group (6.4% vs. 19.7%; HRs: 0.355 [95% CI: 0.191 to 0.662; $p = 0.002$] and 0.335 [95% CI: 0.162 to 0.693; $p = 0.003$] before and after adjustment, respectively). Gynecomastia or breast pain was reported in 16 patients (10.2%) in the treatment group. Serious hyperkalemia led to treatment discontinuation in 3 patients (1.9%).

CONCLUSIONS Aldosterone receptor blockade using spironolactone may substantially reduce the risk of both CCV morbidity and death among HD patients; however, larger-scale studies are recommended to further confirm its efficacy. (Effects of Spironolactone on Cardio- and Cerebrovascular Morbidity and Mortality in Hemodialysis Patients; NCT01687699) (44).

Angiotensin-Converting Enzyme Inhibitor, Angiotensin Receptor Blocker Use, and Mortality in Patients With Chronic Kidney Disease

M.Z. Molnar, et al.

OBJECTIVES The study objective was to assess the association between angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) use and mortality in patients with chronic kidney disease (CKD).

BACKGROUND There is insufficient evidence about the association of ACEI or ARBs with mortality in patients with CKD.

METHODS A logistic regression analysis was used to calculate the propensity of ACEI/ARB initiation in 141,413 U.S. veterans with nondialysis CKD who were previously unexposed to ACEI/ARB treatment. We examined the association of ACEI/ARB administration with all-cause mortality in patients matched by propensity scores using the Kaplan-Meier method and Cox models in “intention-to-treat” analyses and in generalized linear models with binary outcomes and inverse probability of treatment weights in “as-treated” analyses.

RESULTS The age of the patients at baseline was 75 ± 10 years, 8% of patients were black, and 22% were diabetic. ACEI/ARB administration was associated with a significantly lower risk of mortality both in the intention-to-treat analysis (hazard ratio: 0.81, 95% confidence interval: 0.78 to 0.84; $p < 0.001$) and the as-treated analysis with inverse probability of treatment weights (odds ratio: 0.37, 95% confidence interval: 0.34 to 0.41; $p < 0.001$). The association of ACEI/ARB treatment with lower risk of mortality was present in all examined subgroups.

CONCLUSIONS In this large contemporary cohort of nondialysis-dependent patients with CKD, ACEI/ARB administration was associated with greater survival (45).

Cardiovascular Disease Mortality in Asian Americans

P.O. Jose, et al.

BACKGROUND Asian Americans are a rapidly growing racial/ethnic group in the United States. Our current understanding of Asian-American cardiovascular disease mortality patterns is distorted by the aggregation of distinct subgroups.

OBJECTIVES The purpose of the study was to examine heart disease and stroke mortality rates in Asian-American subgroups to determine racial/ethnic differences in cardiovascular disease mortality within the United States.

METHODS We examined heart disease and stroke mortality rates for the 6 largest Asian-American subgroups (Asian Indian, Chinese, Filipino, Japanese, Korean, and Vietnamese) from 2003 to 2010. U.S. death records were used to identify race/ethnicity and cause of death by International Classification of Diseases-10th revision coding. Using both U.S. Census data and death record data, standardized mortality ratios (SMRs), relative SMRs (rSMRs), and proportional mortality ratios were calculated for each sex and ethnic group relative to non-Hispanic whites (NHWs).

RESULTS In this study, 10,442,034 death records were examined. Whereas NHW men and women had the highest overall mortality rates, Asian Indian men and women and Filipino men had greater proportionate mortality burden from ischemic heart disease. The proportionate mortality burden of hypertensive heart disease and cerebrovascular disease, especially hemorrhagic stroke, was higher in every Asian-American subgroup compared with NHWs.

CONCLUSIONS The heterogeneity in cardiovascular disease mortality patterns among diverse Asian-American subgroups calls attention to the need for more research to help direct more specific treatment and prevention efforts, in particular with hypertension and stroke, to reduce health disparities for this growing population (46).

Vaccine for Atherosclerosis

P.K. Shah, et al.

Atherosclerosis is an immune-mediated inflammatory disease of the arterial wall, with both the innate and adaptive immune systems responding to many endogenous and exogenous antigens. Both pro-atherogenic as well as atheroprotective roles have been identified for the immune system in atherosclerosis. Hence, it is conceivable that an immunomodulatory strategy via active immunization against many of these antigens could potentially alter the natural history of atherosclerosis. This review discusses: 1) the complex role of important components of the innate and adaptive immune systems in atherogenesis; 2) the nature of many antigens that have been tested successfully in vaccine formulations to reduce atherosclerosis in pre-clinical experimental models; and 3) the potential opportunities and challenges for clinical application of vaccination for atherosclerosis in the future (47).

Do Current Clinical Trials Meet Society's Needs? A Critical Review of Recent Evidence

S.J. Pocock, et al.

This paper describes some important controversies regarding the current state of clinical trials research in cardiology. Topics covered include the inadequacy of trial research on medical devices, problems with industry-sponsored trials, the lack of head-to-head trials of new effective treatments, the need for wiser handling of drug safety issues, the credibility (or lack thereof) of trial reports in medical journals, problems with globalization of trials, the role of personalized (stratified) medicine in trials, the need for new trials of old drugs, the need for trials of treatment withdrawal, the importance of pragmatic trials of treatment strategies, and the limitations of observational comparative effectiveness studies. All issues are illustrated by recent topical trials in cardiology. Overall, we explore the extent to which clinical trials, as currently practiced, are successful in meeting society's expectations (48).

Trends in Acute Myocardial Infarction in Young Patients and Differences by Sex and Race, 2001 to 2010

A. Gupta, et al.

BACKGROUND Various national campaigns launched in recent years have focused on young women with acute myocardial infarctions (AMIs). Contemporary longitudinal data about sex differences in clinical characteristics, hospitalization rates, length of stay (LOS), and mortality have not been examined.

OBJECTIVES This study sought to determine sex differences in clinical characteristics, hospitalization rates, LOS, and in-hospital mortality by age group and race among young patients with AMIs using a large national dataset of U.S. hospital discharges.

METHODS Using the National Inpatient Sample, clinical characteristics, AMI hospitalization rates, LOS, and in-hospital mortality were compared for patients with AMI across ages 30 to 54 years, dividing them into 5-year subgroups from 2001 to 2010, using survey data analysis techniques.

RESULTS A total of 230,684 hospitalizations were identified with principal discharge diagnoses of AMI in 30- to 54-year-old patients from Nationwide Inpatient Sample data, representing an estimated 1,129,949 hospitalizations in the United States from 2001 to 2010. No statistically significant declines in AMI hospitalization rates were observed in the age groups <55 years or stratified by sex. Prevalence of comorbidities was higher in women and increased among both sexes through the study period. Women had longer LOS and higher in-hospital mortality than men across all age groups. However, observed in-hospital mortality declined significantly for women from 2001 to 2010 (from 3.3% to 2.3%, relative change 30.5%; p for trend < 0.0001) but not for men (from 2% to 1.8%, relative change 8.6%; p for trend = 0.60).

CONCLUSIONS AMI hospitalization rates for young people have not declined over the past decade. Young women with AMIs have more comorbidity, longer LOS, and higher in-hospital mortality than young men, although their mortality rates are decreasing (49).

CARDIAC FAILURE

Pre-Clinical Diastolic Dysfunction

S.-H. Wan, et al.

Pre-clinical diastolic dysfunction (PDD) has been broadly defined as left ventricular diastolic dysfunction without the diagnosis of congestive heart failure (HF) and with normal systolic function. PDD is an entity that remains poorly understood, yet has definite clinical significance. Although few original studies have focused on PDD, it has been shown that PDD is prevalent, and that there is a clear progression from PDD to symptomatic HF including dyspnea, edema, and fatigue. In diabetic patients and in patients with coronary artery disease or hypertension, it has been shown that patients with PDD have a significantly higher risk of progression to heart failure and death compared with patients without PDD. Because of these findings and the increasing prevalence of the heart failure epidemic, it is clear that an understanding of PDD is essential to decreasing patients' morbidity and mortality. This review will focus on what is known concerning pre-clinical diastolic dysfunction, including definitions, staging, epidemiology, pathophysiology, and the natural history of the disease. In addition, given the paucity of trials focused on PDD treatment, studies targeting risk factors associated with the development of PDD and therapeutic trials for heart failure with preserved ejection fraction will be reviewed (50).

Noncardiac Comorbidities in Heart Failure With Reduced Versus Preserved Ejection Fraction

R.J. Mentz, et al.

Heart failure patients are classified by ejection fraction (EF) into distinct groups: heart failure with preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction (HFrEF). Although patients with heart failure commonly have multiple comorbidities that complicate management and may adversely affect outcomes, their role in the HFpEF and HFrEF groups is not well-characterized. This review summarizes the role of noncardiac comorbidities in patients with HFpEF versus HFrEF, emphasizing prevalence, underlying pathophysiologic mechanisms, and outcomes. Pulmonary disease, diabetes mellitus, anemia, and obesity tend to be more prevalent in HFpEF patients, but renal disease and sleep-disordered breathing burdens are similar. These comorbidities similarly increase morbidity and mortality risk in HFpEF and HFrEF patients. Common pathophysiologic mechanisms include systemic and endomyocardial inflammation with fibrosis. We also discuss implications for clinical care and future HF clinical trial design. The basis for this review was discussions between scientists, clinical trialists, and regulatory representatives at the 10th Global Cardio Vascular Clinical Trialists Forum (51).

Head-to-Head Comparison of 2 Myocardial Fibrosis Biomarkers for Long-Term Heart Failure Risk Stratification: ST2 Versus Galectin-3

A. Bayes-Genis, et al.

OBJECTIVES ST2 and galectin-3 (Gal-3) were compared head-to-head for long-term risk stratification in an ambulatory heart failure (HF) population on top of other risk factors including N-terminal pro–B-type natriuretic peptide.

BACKGROUND ST2 and Gal-3 are promising biomarkers of myocardial fibrosis and remodeling in HF.

METHODS This cohort study included 876 patients (median age: 70 years, median left ventricular ejection fraction: 34%). The 2 biomarkers were evaluated relative to conventional assessment (11 risk factors) plus N-terminal pro–B-type natriuretic peptide in terms of discrimination, calibration, and reclassification analysis. Endpoints were 5-year all-cause and cardiovascular mortality, and the combined all-cause death/HF hospitalization.

RESULTS During a median follow-up of 4.2 years (5.9 for alive patients), 392 patients died. In bivariate analysis, Gal-3 and ST2 were independent variables for all endpoints. In multivariate analysis, only ST2 remained independently associated with cardiovascular mortality (hazard ratio: 1.27, 95% confidence interval [CI]: 1.05 to 1.53, $p = 0.014$). Incorporation of ST2 into a full-adjusted model for all-cause mortality (including clinical variables and N-terminal pro–B-type natriuretic peptide) improved discrimination (C-statistic: 0.77, $p = 0.004$) and calibration, and reclassified significantly better (integrated discrimination improvement: 1.5, 95% CI: 0.5 to 2.5, $p = 0.003$; net reclassification index: 9.4, 95% CI: 4.8 to 14.1, $p < 0.001$). Incorporation of Gal-3 showed no significant increase in discrimination or reclassification and worse calibration metrics. On direct model comparison, ST2 was superior to Gal-3.

CONCLUSIONS Head-to-head comparison of fibrosis biomarkers ST2 and Gal-3 in chronic HF revealed superiority of ST2 over Gal-3 in risk stratification. The incremental predictive contribution of Gal-3 to existing clinical risk factors was trivial (52).

Intestinal Blood Flow in Patients With Chronic Heart Failure: A Link With Bacterial Growth, Gastrointestinal Symptoms, and Cachexia

A. Sandek, et al.

BACKGROUND Blood flow in the intestinal arteries is reduced in patients with stable heart failure (HF) and relates to gastrointestinal (GI) symptoms and cardiac cachexia.

OBJECTIVES The aims of this study were to measure arterial intestinal blood flow and assess its role in juxtamucosal bacterial growth, GI symptoms, and cachexia in patients with HF.

METHODS A total of 65 patients and 25 controls were investigated. Twelve patients were cachectic. Intestinal blood flow and bowel wall thickness were measured using ultrasound. GI symptoms were documented. Bacteria in stool and juxtamucosal bacteria on biopsies taken during sigmoidoscopy were studied in a subgroup by fluorescence in situ hybridization. Serum lipopolysaccharide antibodies were measured.

RESULTS Patients showed 30% to 43% reduced mean systolic blood flow in the superior and inferior mesenteric arteries and celiac trunk (CT) compared with controls ($p < 0.007$ for all). Cachectic patients had the lowest blood flow ($p < 0.002$). Lower blood flow in the superior mesenteric artery and CT was correlated with HF severity ($p < 0.04$ for all). Patients had more feelings of repletion, flatulence, intestinal murmurs, and burping ($p < 0.04$). Burping and nausea or vomiting were most severe in patients with cachexia ($p < 0.05$). Patients with lower CT blood flow had more abdominal discomfort and immunoglobulin A–antilipopolysaccharide ($r = 0.76$, $p < 0.02$). Antilipopolysaccharide response was correlated with increased growth of juxtamucosal but not stool bacteria. Patients with intestinal murmurs had greater bowel wall thickness of the sigmoid and descending colon, suggestive of edema contributing to GI symptoms ($p < 0.05$). In multivariate regression analysis, lower blood flow in the superior mesenteric artery, CT ($p < 0.04$), and inferior mesenteric artery ($p = 0.056$) was correlated with the presence of cardiac cachexia.

CONCLUSIONS Intestinal blood flow is reduced in patients with HF. This may contribute to juxtamucosal bacterial growth and GI symptoms in patients with advanced HF complicated by cachexia (53).

Prognostic Value of Elevated Levels of Intestinal Microbe-Generated Metabolite Trimethylamine-*N*-Oxide in Patients With Heart Failure: Refining the Gut Hypothesis

W.H. Wilson Tang, et al.

BACKGROUND Altered intestinal function is prevalent in patients with heart failure (HF), but its role in adverse outcomes is unclear.

OBJECTIVES This study investigated the potential pathophysiological contributions of intestinal microbiota in HF.

METHODS We examined the relationship between fasting plasma trimethylamine-*N*-oxide (TMAO) and all-cause mortality over a 5-year follow-up in 720 patients with stable HF.

RESULTS The median TMAO level was 5.0 μM, which was higher than in subjects without HF (3.5 μM; $p < 0.001$). There was modest but significant correlation between TMAO concentrations and B-type natriuretic peptide (BNP) levels ($r = 0.23$; $p < 0.001$). Higher plasma TMAO levels were associated with a 3.4-fold increased mortality risk. Following adjustments for traditional risk factors and BNP levels, elevated TMAO levels remained predictive of 5-year mortality risk (hazard ratio [HR]: 2.2; 95% CI: 1.42 to 3.43; $p < 0.001$), as well as following the addition of estimated glomerular filtration rate to the model (HR: 1.75; 95% CI: 1.07 to 2.86; $p < 0.001$).

CONCLUSIONS High TMAO levels were observed in patients with HF, and elevated TMAO levels portended higher long-term mortality risk independent of traditional risk factors and cardiorenal indexes (54).

The Use of Digoxin in Patients With Worsening Chronic Heart Failure: Reconsidering an Old Drug to Reduce Hospital Admissions

A.P. Ambrosy, et al.

Digoxin is the oldest cardiac drug still in contemporary use, yet its role in the management of patients with heart failure (HF) remains controversial. A purified cardiac glycoside derived from the foxglove plant, digoxin increases ejection fraction, augments cardiac output, and reduces pulmonary capillary wedge pressure without causing deleterious increases in heart rate or decreases in blood pressure. Moreover, it is also a neurohormonal modulator at low doses. In the pivotal DIG (Digitalis Investigation Group) trial, digoxin therapy was shown to reduce all-cause and HF-specific hospitalizations but had no effect on survival. With the discovery of neurohormonal blockers capable of reducing mortality in HF with reduced ejection fraction, the results of the DIG trial were viewed as neutral, and the use of digoxin declined precipitously. Although modern drug and device-based therapies have dramatically improved the survival of ambulatory patients with HF, outcomes for patients with worsening chronic HF, defined as deteriorating signs and symptoms on standard therapy often leading to unscheduled clinic or emergency department visits or hospitalization, have largely remained unchanged over the past 2 decades. The available data suggest that a therapeutic trial of digoxin may be appropriate in patients with worsening chronic heart failure who remain symptomatic (55).

Current Evidence on Treatment of Patients With Chronic Systolic Heart Failure and Renal Insufficiency: Practical Considerations From Published Data

K. Damman, et al.

Chronic kidney disease (CKD) is increasingly prevalent in patients with chronic systolic heart failure. Therefore, evidence-based therapies are more and more being used in patients with some degree of renal dysfunction. However, most pivotal randomized clinical trials specifically excluded patients with (severe) renal dysfunction. The benefit of these evidence-based therapies in this high-risk patient group is largely unknown. This paper reviews data from randomized clinical trials in systolic heart failure and the interactions between baseline renal dysfunction and the effect of randomized treatment. It highlights that most evidence-based therapies show consistent outcome benefit in patients with moderate renal insufficiency (stage 3 CKD), whereas there are very scarce data on patients with severe (stage 4 to 5 CKD) renal insufficiency. If any, the outcome benefit might be even greater in stage 3 CKD compared with those with relatively preserved renal function. However, prescription of therapies should be individualized with consideration of possible harm and benefit, especially in those with stage 4 to 5 CKD where limited data are available (56).

Inotropes

G.S. Francis, et al.

Inotropes have been fundamental to resuscitation of acute cardiogenic shock for decades. Heart failure and cardiogenic shock, in severe cases, are syndromes characterized in many patients by a reduction in myocardial contractile force. While inotropes successfully increase cardiac output, their use has been plagued by excessive mortality due to increased tachycardia and myocardial oxygen consumption leading to arrhythmia and myocardial ischemia. There is a pressing need for new inotropic agents that avoid these harmful effects. This review describes the mechanism of action and the clinical utility of some

of the older inotropic agents, which are still commonly used, and provides an update for physicians on the development of newer inotropic drugs. The field is rapidly changing, and it is likely that new agents will be designed that improve systolic performance without necessarily increasing the myocardial oxygen consumption (57).

Results of the Destination Therapy Post-Food and Drug Administration Approval Study With a Continuous Flow Left Ventricular Assist Device: A Prospective Study Using the INTERMACS Registry (Interagency Registry for Mechanically Assisted Circulatory Support)

U.P. Jorde, et al.

OBJECTIVES A post-approval (PA) study for destination therapy (DT) was required by the Food and Drug Administration (FDA) to determine whether results with the HeartMate (HM) II (Thoratec, Pleasanton, California) left ventricular assist device (LVAD) in a commercial setting were comparable to results during the DT multicenter pivotal clinical trial.

BACKGROUND New device technology developed in the clinical research setting requires validation in a real-world setting.

METHODS The PA study was a prospective evaluation of the first 247 HM II patients identified preoperatively as eligible for DT in the national INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry. Patients were enrolled from January to September 2010 at 61 U.S. centers and followed for 2 years. A historical comparison group included patients (n = 133 at 34 centers) enrolled in the primary data cohort in the DT pivotal trial (TR). Survival rates and adverse events for the PA group were obtained from the INTERMACS registry.

RESULTS Baseline characteristics were similar for PA versus TR. Forty-five percent of PA patients were in INTERMACS profiles 1 to 2 and 28% were in profile 3. Adverse events in the PA group were similar or lower than those in the TR group, including improvements in device-related infection (0.22 vs. 0.47) and post-operative bleeding requiring surgery (0.09 vs. 0.23) events per patient-year. Kaplan-Meier survival at 2 years was 62% (PA group) versus 58% (TR group). PA group survival at 1 and 2 years was 82 ± 5% and 69 ± 6% for INTERMACS profiles 4 to 7 (n = 63) versus 72 ± 3% and 60 ± 4% for profiles 1 to 3 (n = 184). The median length of stay after surgery was reduced by 6 days in the PA group versus the TR group.

CONCLUSIONS Results in a commercial patient care setting for the DT population supported the original pivotal clinical trial findings regarding the efficacy and risk profile of the HM II LVAD. Survival was best in patients who were not inotrope-dependent (INTERMACS profiles 4 to 7) (58).

Antithrombotic Treatment in Patients With Heart Failure and Associated Atrial Fibrillation and Vascular Disease: A Nationwide Cohort Study

M. Lamberts, et al.

OBJECTIVES The aim of this study was to investigate the impact of atrial fibrillation (AF) and antithrombotic treatment on the prognosis in patients with heart failure (HF) as well as vascular disease.

BACKGROUND HF, vascular disease, and AF are pathophysiologically related, and understanding antithrombotic treatment for these conditions is crucial.

METHODS In hospitalized patients with HF and coexisting vascular disease (coronary artery disease or peripheral arterial disease) followed from 1997 to 2009, AF status was categorized as prevalent AF, incident AF, or no AF. Risk of thromboembolism (TE), myocardial infarction (MI), and serious bleeding was assessed by Cox regression models (hazard ratio [HR] with 95% confidence interval [CI]) with antithrombotic therapy and AF as time-dependent variables.

RESULTS A total of 37,464 patients were included (age, 74.5 ± 10.7 years; 36.3% females) with a mean follow-up of 3 years during which 20.7% were categorized as prevalent AF and 17.2% as incident AF. Compared with vitamin K antagonist (VKA) in prevalent AF, VKA plus antiplatelet was not associated with a decreased risk of TE (HR: 0.91; 95% CI: 0.73 to 1.12) or MI (HR: 1.11; 95% CI: 0.96 to 1.28), whereas bleeding risk was significantly increased (HR: 1.31; 95% CI: 1.09 to 1.57). Corresponding estimates for incident AF were HRs of 0.77 (95% CI: 0.56 to 1.06), 1.07 (95% CI: 0.89 to 1.28), and 2.71 (95% CI: 1.33 to 2.21) for TE, MI, and bleeding, respectively. In no AF patients, no statistical differences were seen between antithrombotic therapies in TE or MI risk, whereas bleeding risk was significantly increased for VKA with and without single-antiplatelet therapy.

CONCLUSIONS In AF patients with coexisting HF and vascular disease, adding single-antiplatelet therapy to VKA therapy is not associated with additional benefit in thromboembolic or coronary risk, but notably increased bleeding risk (59).

Extracorporeal Membrane Oxygenation in Cardiopulmonary Disease in Adults

D. Abrams, et al.

The use of extracorporeal membrane oxygenation (ECMO) for both respiratory and cardiac failure in adults is evolving rapidly. Advances in technology and accumulating data are spurring greater interest and explosive growth in ECMO worldwide. Expanding indications and novel strategies are being used. Yet the use of ECMO outpaces the data. The promise of a major paradigm shift for the treatment of respiratory and cardiac failure is tempered by a need for evidence to support many current and potential future uses. The authors review cannulation strategies, indications, and evidence for ECMO in respiratory and cardiac failure in adults as well as potential applications and the impact they may have on current treatment paradigms (60).

Clinical Impact of Atrial Fibrillation in Patients With the HeartMate II Left Ventricular Assist Device

A.D. Enriquez, et al.

BACKGROUND Atrial fibrillation (AF) is common in patients with the HeartMate II (HMII) left ventricular assist device (LVAD), but the impact of AF on clinical outcomes is uncertain.

OBJECTIVES This study sought to determine the effect of AF on outcomes in patients with the HMII LVAD.

METHODS Records of 106 patients who underwent HMII implantation at a single center were reviewed. The associations of paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation (PeAF) with survival, heart failure (HF) hospitalization, bleeding, and thromboembolism were examined using Kaplan-Meier survival analysis and Cox proportional hazards regression.

RESULTS Mean age was 56.6 ± 11.4 years, 87.7% of the implants were intended as a bridge to transplantation, and median length of support was 217 days (range: 1 to 952 days). AF was present in 55 patients (51.9%); 36 patients (34.0%) had PAF and 19 (17.9%) had PeAF. Twenty-one patients (19.8%) died, and 18 (17.0%) were hospitalized for HF. There were 0.75 major bleeding events and 0.28 thromboembolic events per patient year of follow-up. PAF was not associated with increased mortality, HF hospitalization, bleeding, or thromboembolism. PeAF, however, was an independent predictor of the composite endpoint of death or HF hospitalization (hazard ratio: 3.54; 95% confidence interval: 1.52 to 8.25; $p < 0.01$). Although there was no increase in bleeding or thromboembolism, patients with AF had thromboembolic events at higher international normalized ratios (INRs).

CONCLUSIONS Although PAF is not associated with worse outcomes in patients with the HMII LVAD, PeAF may be associated with increased mortality and HF hospitalization. Patients with AF also may have thromboembolic events at higher INR levels (61).

Survival Benefit From Transplantation in Patients Listed for Heart Transplantation in the United States

T.P. Singh, et al.

OBJECTIVES The aim of this study was to assess the survival benefit from heart transplantation (HT), defined as reduction in the risks for 90-day and 1-year mortality on undergoing HT close to listing, in candidates stratified by their risk for waiting list mortality.

BACKGROUND Among patients listed for HT, those at higher risk for death without transplantation are also at higher risk for early post-transplantation mortality.

METHODS All patients age ≥18 years listed for HT in the United States from 2007 to 2010 were analyzed. A model was developed to predict the risk for waiting list mortality within 90 days, and listed patients were stratified into 10 risk groups (deciles). All groups were followed for 1 year to assess cumulative 1-year mortality while on the waiting list. Models of 90-day and 1-year post-transplantation mortality were developed using recipient data, and these risks were estimated at listing in all listed candidates.

RESULTS Of 10,159 patients listed for HT, 596 (5.9%) died within 90 days and 1,054 (10.4%) within 1 year without undergoing transplantation. Of 5,720 recipients of transplants with 1-year follow-up, 576 (10.1%) died within 1 year. The risk for death while on the waiting list within 90 days increased from 1.6% to 19% across the 10 risk groups. The survival benefit from HT increased progressively with higher risk for death without transplantation ($p < 0.001$ for trend), but there was no benefit in the first 6 risk groups.

CONCLUSIONS The risk for waiting list mortality varies considerably among HT candidates. Although the survival benefit of HT generally increases with increasing risk for waiting list mortality, there is no measurable benefit in many candidates at the lower end of the risk spectrum (62).

JACC VOL. 65, NO. 6, 2015
FEBRUARY 17, 2015:586–614

CARDIOMYOPATHIES

The MOGE(S) Classification of Cardiomyopathy for Clinicians

E. Arbustini, et al.

Most cardiomyopathies are familial diseases. Cascade family screening identifies asymptomatic patients and family members with early traits of disease. The inheritance is autosomal dominant in a majority of cases, and recessive, X-linked, or matrilinear in the remaining. For the last 50 years, cardiomyopathy classifications have been based on the morphofunctional phenotypes, allowing cardiologists to conveniently group them in broad descriptive categories. However, the phenotype may not always conform to the genetic characteristics, may not allow risk stratification, and may not provide pre-clinical diagnoses in the family members. Because genetic testing is now increasingly becoming a part of clinical work-up, and based on the genetic heterogeneity, numerous new names are being coined for the description of cardiomyopathies associated with mutations in different genes; a comprehensive nosology is needed that could inform the clinical phenotype and involvement of organs other than the heart, as well as the genotype and the mode of inheritance. The recently proposed MOGE(S) nosology system embodies all of these characteristics, and describes the morphofunctional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), etiological annotation (E) including genetic defect or underlying disease/substrate, and the functional status (S) of the disease using both the American College of Cardiology/American Heart Association stage and New York Heart Association functional class. The proposed nomenclature is supported by a web-assisted application and assists in the description of cardiomyopathy in symptomatic or asymptomatic patients and family members in the context of genetic testing. It is expected that such a nomenclature would help group cardiomyopathies on their etiological basis, describe complex genetics, and create collaborative registries (63).

Hypertrophic Cardiomyopathy: Present and Future, With Translation Into Contemporary Cardiovascular Medicine

B.J. Maron, et al.

Hypertrophic cardiomyopathy (HCM) is a common inherited heart disease with diverse phenotypic and genetic expression, clinical presentation, and natural history. HCM has been recognized for 55 years, but recently substantial advances in diagnosis and treatment options have evolved, as well as increased recognition of the disease in clinical practice. Nevertheless, most genetically and clinically affected individuals probably remain undiagnosed, largely free from disease-related complications, although HCM may progress along 1 or more of its major disease pathways (i.e, arrhythmic sudden death risk; progressive heart failure [HF] due to dynamic left ventricular [LV] outflow obstruction or due to systolic dysfunction in the absence of obstruction; or atrial fibrillation with risk of stroke). Effective treatments are available for each adverse HCM complication, including implantable cardioverter-defibrillators (ICDs) for sudden death prevention, heart transplantation for end-stage failure, surgical myectomy (or selectively, alcohol septal ablation) to alleviate HF symptoms by abolishing outflow obstruction, and catheter-based procedures to control atrial fibrillation. These and other strategies have now resulted in a low disease-related mortality rate of <1%/year. Therefore, HCM has emerged from an era of misunderstanding, stigma, and pessimism, experiencing vast changes in its clinical profile, and acquiring an effective and diverse management armamentarium. These advances have changed its natural history, with prevention of sudden death and reversal of HF, thereby restoring quality of life with extended (if not normal) longevity for most patients, and transforming HCM into a contemporary treatable cardiovascular disease (64).

Left Ventricular Noncompaction: A Distinct Cardiomyopathy or a Trait Shared by Different Cardiac Diseases?

E. Arbustini, et al.

Whether left ventricular noncompaction (LVNC) is a distinct cardiomyopathy or a morphologic trait shared by different cardiomyopathies remains controversial. Current guidelines from professional organizations recommend different strategies for diagnosing and treating patients with LVNC. This state-of-the-art review discusses new insights into the basic mechanisms leading to LVNC, its clinical manifestations, treatment modalities, anatomy and pathology, embryology, genetics, epidemiology, and imaging. Three markers currently define LVNC: prominent left ventricular trabeculae, deep intertrabecular recesses, and a thin compacted layer. Although new genetic data from mice and humans supports LVNC as a distinct

cardiomyopathy, evidence for LVNC as a shared morphological trait is not ruled out. Criteria supporting LVNC as a shared morphological trait may depend on consensus guidelines from the multiple professional organizations. Enhanced imaging and increased use of genetics are both predicted to significantly impact our overall understanding of the basic mechanisms causing LVNC and its optimal management (65).

Recovery of Echocardiographic Function in Children With Idiopathic Dilated Cardiomyopathy: Results From the Pediatric Cardiomyopathy Registry

M.D. Everitt, et al.

OBJECTIVES This study sought to determine the incidence and predictors of recovery of normal echocardiographic function among children with idiopathic dilated cardiomyopathy (DCM).

BACKGROUND Most children with idiopathic DCM have poor outcomes; however, some improve.

METHODS We studied children <18 years of age from the Pediatric Cardiomyopathy Registry who had both depressed left ventricular (LV) function (fractional shortening or ejection fraction *z*-score <-2) and LV dilation (end-diastolic dimension [LVEDD] *z*-score >2) at diagnosis and who had at least 1 follow-up echocardiogram 30 days to 2 years from the initial echocardiogram. We estimated the cumulative incidence and predictors of normalization.

RESULTS Among 868 children who met the inclusion criteria, 741 (85%) had both echocardiograms. At 2 years, 22% had recovered normal LV function and size; 51% had died or undergone heart transplantation (median, 3.2 months), and 27% had persistently abnormal echocardiograms. Younger age (hazard ratio [HR]: 0.92; 95% confidence interval [CI]: 0.88 to 0.97) and lower LVEDD *z*-score (HR: 0.78; 95% CI: 0.70 to 0.87) independently predicted normalization. Nine children (9%) with normal LV function and size within 2 years of diagnosis later underwent heart transplantation or died.

CONCLUSIONS Despite marked LV dilation and depressed function initially, children with idiopathic DCM can recover normal LV size and function, particularly those younger and with less LV dilation at diagnosis. Investigations related to predictors of recovery, such as genetic associations, serum markers, and the impact of medical therapy or ventricular unloading with assist devices are important next steps. Longer follow-up after normalization is warranted as cardiac failure can recur. (Pediatric Cardiomyopathy Registry; NCT00005391) (66).

Contribution of the Diastolic Vortex Ring to Left Ventricular Filling

P. Martínez-Legazpi, et al.

BACKGROUND Intraventricular fluid dynamics can be assessed clinically using imaging. The contribution of vortex structures to left ventricular (LV) diastolic function has never been quantified in vivo.

OBJECTIVES This study sought to understand the impact of intraventricular flow patterns on filling and to assess whether impaired fluid dynamics may be a source of diastolic dysfunction.

METHODS Two-dimensional flow velocity fields from color Doppler echocardiographic sequences were obtained in 20 patients with nonischemic dilated cardiomyopathy (NIDCM), 20 patients with hypertrophic cardiomyopathy (HCM), and 20 control healthy volunteers. Using a flow decomposition method, we isolated the rotational velocity generated by the vortex ring from the surrounding flow in the left ventricle.

RESULTS The vortex was responsible for entering 13 ± 6% of filling volume in the control group and 19 ± 8% in the NIDCM group ($p = 0.004$), but only 5 ± 5% in the HCM group ($p < 0.0001$ vs. controls). Favorable vortical effects on intraventricular pressure gradients were observed in the control and NIDCM groups but not in HCM patients. Differences in chamber sphericity explained variations in the vortex contribution to filling between groups ($p < 0.005$).

CONCLUSIONS The diastolic vortex is responsible for entering a significant fraction of LV filling volume at no energetic or pressure cost. Thus, intraventricular fluid mechanics are an important determinant of global chamber LV operative stiffness. Reduced stiffness in NIDCM is partially related to enhanced vorticity. Conversely, impaired vortex generation is an unreported mechanism of diastolic dysfunction in HCM and probably other causes of concentric remodeling (67).

Prevention of Anthracycline-Induced Cardiotoxicity: Challenges and Opportunities

P. Vejpongsa, et al.

Anthracycline compounds are major culprits in chemotherapy-induced cardiotoxicity, which is the chief limiting factor in delivering optimal chemotherapy to cancer patients. Although extensive efforts have been devoted to identifying strategies to prevent anthracycline-induced cardiotoxicity, there is little consensus regarding the best approach. Recent

advances in basic mechanisms of anthracycline-induced cardiotoxicity provided a unified theory to explain the old reactive-oxygen species hypothesis and identified topoisomerase 2β as the primary molecular target for cardioprotection. This review outlines current strategies for primary and secondary prevention of anthracycline-induced cardiotoxicity resulting from newly recognized molecular mechanisms and identifies knowledge gaps requiring further investigation (68).

Vector Flow Mapping in Obstructive Hypertrophic Cardiomyopathy to Assess the Relationship of Early Systolic Left Ventricular Flow and the Mitral Valve

R. Ro, et al.

BACKGROUND The hydrodynamic cause of systolic anterior motion of the mitral valve (SAM) is unresolved.

OBJECTIVES This study hypothesized that echocardiographic vector flow mapping, a new echocardiographic technique, would provide insights into the cause of early SAM in obstructive hypertrophic cardiomyopathy (HCM).

METHODS We analyzed the spatial relationship of left ventricular (LV) flow and the mitral valve leaflets (MVL) on 3-chamber vector flow mapping frames, and performed mitral valve measurements on 2-dimensional frames in patients with obstructive and nonobstructive HCM and in normal patients.

RESULTS We compared 82 patients (22 obstructive HCM, 23 nonobstructive HCM, and 37 normal) by measuring 164 LV pre- and post-SAM velocity vector flow maps, 82 maximum isovolumic vortices, and 328 2-dimensional frames. We observed color flow and velocity vector flow posterior to the MVL impacting them in the early systolic frames of 95% of obstructive HCM, 22% of nonobstructive HCM, and 11% of normal patients ($p < 0.001$). In both pre- and post-SAM frames, we measured a high angle of attack $>60^{\circ}$ of local vector flow onto the posterior surface of the leaflets whether the flow was ejection (59%) or the early systolic isovolumic vortex (41%). Ricochet of vector flow, rebounding off the leaflet into the cul-de-sac, was noted in 82% of the obstructed HCM, 9% of nonobstructive HCM, and none (0%) of the control patients ($p < 0.001$). Flow velocities in the LV outflow tract on the pre-SAM frame 1 and 2 mm from the tip of the anterior leaflet were low: 39 and 43 cm/s, respectively.

CONCLUSIONS Early systolic flow impacts the posterior surfaces of protruding MVL initiating SAM in obstructive HCM (69).

Peripartum Cardiomyopathy: Predictors of Recovery and Current State of Implantable Cardioverter-Defibrillator Use

J. Pillarisetti, et al.

OBJECTIVES The purpose of this study was to identify the predictors of left ventricular (LV) recovery in patients with peripartum cardiomyopathy (PPCM) and to record rates of implantable cardioverter-defibrillator (ICD) use.

BACKGROUND PPCM is a rare, life-threatening disease. The use of ICDs has not been clearly understood in this patient group. Identification of the predictors of persistent LV dysfunction can help select patients at risk for sudden cardiac death.

METHODS A retrospective study was conducted at 2 academic centers between January 1, 1999, and December 31, 2012. Clinical and demographic variables and delivery records of patients with a diagnosis of PPCM (*International Classification of Diseases, 9th Revision* code 674.5) were reviewed. Improvement in LV function was noted from echocardiography reports.

RESULTS The total sample comprised 100 patients, of whom 55% were African Americans, 39% were Caucasians, and 6% were Hispanic, with a mean age of 30 ± 6 years. Mean left ventricular ejection fraction (LVEF) at diagnosis was $28 \pm 9\%$. Forty-two percent of patients showed improvement in LVEF over a mean duration of 33 ± 21 months. Postpartum diagnosis (hazard ratio: 3.0; $p = 0.01$) and Caucasian/Hispanic race (hazard ratio: 2.2; $p = 0.01$) were predictors of improvement in LVEF. Only 7 of the 58 patients (12%) who did not have improvement in their LVEF had an ICD implanted. There were 11 deaths, with a trend toward higher mortality in those who did not display improved LV function (15% vs. 5%; $p = 0.1$).

CONCLUSIONS More than one-third of women with PPCM improve LV function with delayed recovery noted in the majority of these patients. Caucasians and those diagnosed in the postpartum period appear to be the most likely to recover. The rate of ICD implantation for primary prevention of sudden cardiac death in this patient group is low (70).

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